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(54) Title: MP53s AS MODIFIERS OF THE p53 PATHWAY AND METHODS OF USE

(57) Abstract: Human MP53 genes are identified as modulators of the p53 pathway, and thus are therapeutic targets for disorders associated with defective p53 function. Methods for identifying modulators of p53, comprising screening for agents that modulate the activity of MP53 are provided.

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MP53s AS MODIFIERS OF THE p53 PATHWAY AND METHODS OF USE

REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. provisional patent application 60/361,196
5 filed 3/1/2002. The contents of the prior applications are hereby incorporated in their entirety.

BACKGROUND OF THE INVENTION

The p53 gene is mutated in over 50 different types of human cancers, including
10 familial and spontaneous cancers, and is believed to be the most commonly mutated gene in human cancer (Zambetti and Levine, FASEB (1993) 7:855-865; Hollstein, *et al.*, Nucleic Acids Res. (1994) 22:3551-3555). Greater than 90% of mutations in the p53 gene are missense mutations that alter a single amino acid that inactivates p53 function. Aberrant forms of human p53 are associated with poor prognosis, more aggressive tumors,
15 metastasis, and short survival rates (Mitsudomi *et al.*, Clin Cancer Res 2000 Oct; 6(10):4055-63; Koshland, Science (1993) 262:1953).

The human p53 protein normally functions as a central integrator of signals including DNA damage, hypoxia, nucleotide deprivation, and oncogene activation (Prives, Cell (1998) 95:5-8). In response to these signals, p53 protein levels are greatly increased
20 with the result that the accumulated p53 activates cell cycle arrest or apoptosis depending on the nature and strength of these signals. Indeed, multiple lines of experimental evidence have pointed to a key role for p53 as a tumor suppressor (Levine, Cell (1997) 88:323-331). For example, homozygous p53 "knockout" mice are developmentally normal but exhibit nearly 100% incidence of neoplasia in the first year of life (Donehower
25 *et al.*, Nature (1992) 356:215-221).

The biochemical mechanisms and pathways through which p53 functions in normal and cancerous cells are not fully understood, but one clearly important aspect of p53 function is its activity as a gene-specific transcriptional activator. Among the genes with known p53-response elements are several with well-characterized roles in either
30 regulation of the cell cycle or apoptosis, including GADD45, p21/Waf1/Cip1, cyclin G, Bax, IGF-BP3, and MDM2 (Levine, Cell (1997) 88:323-331).

The ability to manipulate the genomes of model organisms such as *Drosophila* provides a powerful means to analyze biochemical processes that, due to significant evolutionary conservation, have direct relevance to more complex vertebrate organisms.

Due to a high level of gene and pathway conservation, the strong similarity of cellular processes, and the functional conservation of genes between these model organisms and mammals, identification of the involvement of novel genes in particular pathways and their functions in such model organisms can directly contribute to the understanding of the correlative pathways and methods of modulating them in mammals (see, for example, 5 Mechler BM et al., 1985 EMBO J 4:1551-1557; Gateff E. 1982 Adv. Cancer Res. 37: 33-74; Watson KL., et al., 1994 J Cell Sci. 18: 19-33; Miklos GL, and Rubin GM. 1996 Cell 86:521-529; Wassarman DA, et al., 1995 Curr Opin Gen Dev 5: 44-50; and Booth DR. 1999 Cancer Metastasis Rev. 18: 261-284). For example, a genetic screen can be carried out in an invertebrate model organism having underexpression (e.g. knockout) or overexpression of a gene (referred to as a "genetic entry point") that yields a visible phenotype. Additional genes are mutated in a random or targeted manner. When a gene mutation changes the original phenotype caused by the mutation in the genetic entry point, the gene is identified as a "modifier" involved in the same or overlapping pathway as the 10 genetic entry point. When the genetic entry point is an ortholog of a human gene implicated in a disease pathway, such as p53, modifier genes can be identified that may be attractive candidate targets for novel therapeutics.

All references cited herein, including patents, patent applications, publications, and sequence information in referenced Genbank identifier numbers, are incorporated herein in 20 their entireties.

SUMMARY OF THE INVENTION

We have discovered genes that modify the p53 pathway in *Drosophila*, and identified their human orthologs, hereinafter referred to as Modifier of p53 (MP53). The invention provides methods for utilizing these p53 modifier genes and polypeptides to 25 identify MP53-modulating agents that are candidate therapeutic agents that can be used in the treatment of disorders associated with defective or impaired p53 function and/or MP53 function. Preferred MP53-modulating agents specifically bind to MP53 polypeptides and restore p53 function. Other preferred MP53-modulating agents are nucleic acid 30 modulators such as antisense oligomers and RNAi that repress MP53 gene expression or product activity by, for example, binding to and inhibiting the respective nucleic acid (i.e. DNA or mRNA).

MP53 modulating agents may be evaluated by any convenient *in vitro* or *in vivo* assay for molecular interaction with an MP53 polypeptide or nucleic acid. In one

embodiment, candidate MP53 modulating agents are tested with an assay system comprising a MP53 polypeptide or nucleic acid. Agents that produce a change in the activity of the assay system relative to controls are identified as candidate p53 modulating agents. The assay system may be cell-based or cell-free. MP53-modulating agents
5 include MP53 related proteins (e.g. dominant negative mutants, and biotherapeutics); MP53 -specific antibodies; MP53 -specific antisense oligomers and other nucleic acid modulators; and chemical agents that specifically bind to or interact with MP53 or compete with MP53 binding partner (e.g. by binding to an MP53 binding partner). In one specific embodiment, a small molecule modulator is identified using a binding assay. In
10 specific embodiments, the screening assay system is selected from an apoptosis assay, a cell proliferation assay, an angiogenesis assay, and a hypoxic induction assay.

In another embodiment, candidate p53 pathway modulating agents are further tested using a second assay system that detects changes in the p53 pathway, such as angiogenic, apoptotic, or cell proliferation changes produced by the originally identified
15 candidate agent or an agent derived from the original agent. The second assay system may use cultured cells or non-human animals. In specific embodiments, the secondary assay system uses non-human animals, including animals predetermined to have a disease or disorder implicating the p53 pathway, such as an angiogenic, apoptotic, or cell proliferation disorder (e.g. cancer).

20 The invention further provides methods for modulating the MP53 function and/or the p53 pathway in a mammalian cell by contacting the mammalian cell with an agent that specifically binds a MP53 polypeptide or nucleic acid. The agent may be a small molecule modulator, a nucleic acid modulator, or an antibody and may be administered to a mammalian animal predetermined to have a pathology associated the p53 pathway.

25

DETAILED DESCRIPTION OF THE INVENTION

Genetic screens were designed to identify modifiers of the p53 pathway in *Drosophila*, where a genetic modifier screen was carried out in which p53 was overexpressed in the wing (Ollmann M, et al., Cell 2000 101: 91-101). Modifiers of the
30 p53 pathway were identified. Accordingly, vertebrate orthologs of these modifiers, and preferably the human orthologs, MP53 genes (i.e., nucleic acids and polypeptides) are attractive drug targets for the treatment of pathologies associated with a defective p53 signaling pathway, such as cancer. Table 1 (Example II) lists the modifiers and their orthologs.

In vitro and in vivo methods of assessing MP53 function are provided herein. Modulation of the MP53 or their respective binding partners is useful for understanding the association of the p53 pathway and its members in normal and disease conditions and for developing diagnostics and therapeutic modalities for p53 related pathologies. MP53-
5 modulating agents that act by inhibiting or enhancing MP53 expression, directly or indirectly, for example, by affecting an MP53 function such as enzymatic (e.g., catalytic) or binding activity, can be identified using methods provided herein. MP53 modulating agents are useful in diagnosis, therapy and pharmaceutical development.

10 **Nucleic acids and polypeptides of the invention**

Sequences related to MP53 nucleic acids and polypeptides that can be used in the invention are disclosed in Genbank (referenced by Genbank identifier (GI) or RefSeq number), and shown in Table 1 (ExampleII).

The term "MP53 polypeptide" refers to a full-length MP53 protein or a
15 functionally active fragment or derivative thereof. A "functionally active" MP53 fragment or derivative exhibits one or more functional activities associated with a full-length, wild-type MP53 protein, such as antigenic or immunogenic activity, enzymatic activity, ability to bind natural cellular substrates, etc. The functional activity of MP53 proteins, derivatives and fragments can be assayed by various methods known to one skilled in the
20 art (Current Protocols in Protein Science (1998) Coligan *et al.*, eds., John Wiley & Sons, Inc., Somerset, New Jersey) and as further discussed below. In one embodiment, a functionally active MP53 polypeptide is a MP53 derivative capable of rescuing defective endogenous MP53 activity, such as in cell based or animal assays; the rescuing derivative may be from the same or a different species. For purposes herein, functionally active
25 fragments also include those fragments that comprise one or more structural domains of an MP53, such as a binding domain. Protein domains can be identified using the PFAM program (Bateman A., et al., Nucleic Acids Res, 1999, 27:260-2). Methods for obtaining MP53 polypeptides are also further described below. In some embodiments, preferred fragments are functionally active, domain-containing fragments comprising at least 25
30 contiguous amino acids, preferably at least 50, more preferably 75, and most preferably at least 100 contiguous amino acids of any one of SEQ ID NOs:57-112 (an MP53). In further preferred embodiments, the fragment comprises the entire functionally active domain.

The term "MP53 nucleic acid" refers to a DNA or RNA molecule that encodes a MP53 polypeptide. Preferably, the MP53 polypeptide or nucleic acid or fragment thereof is from a human, but can also be an ortholog, or derivative thereof with at least 70% sequence identity, preferably at least 80%, more preferably 85%, still more preferably 90%, and most preferably at least 95% sequence identity with human MP53. Methods of identifying orthologs are known in the art. Normally, orthologs in different species retain the same function, due to presence of one or more protein motifs and/or 3-dimensional structures. Orthologs are generally identified by sequence homology analysis, such as BLAST analysis, usually using protein bait sequences. Sequences are assigned as a potential ortholog if the best hit sequence from the forward BLAST result retrieves the original query sequence in the reverse BLAST (Huynen MA and Bork P, Proc Natl Acad Sci (1998) 95:5849-5856; Huynen MA *et al.*, Genome Research (2000) 10:1204-1210). Programs for multiple sequence alignment, such as CLUSTAL (Thompson JD et al, 1994, Nucleic Acids Res 22:4673-4680) may be used to highlight conserved regions and/or residues of orthologous proteins and to generate phylogenetic trees. In a phylogenetic tree representing multiple homologous sequences from diverse species (e.g., retrieved through BLAST analysis), orthologous sequences from two species generally appear closest on the tree with respect to all other sequences from these two species. Structural threading or other analysis of protein folding (e.g., using software by ProCeryon, Biosciences, Salzburg, Austria) may also identify potential orthologs. In evolution, when a gene duplication event follows speciation, a single gene in one species, such as *Drosophila*, may correspond to multiple genes (paralogs) in another, such as human. As used herein, the term "orthologs" encompasses paralogs. As used herein, "percent (%) sequence identity" with respect to a subject sequence, or a specified portion of a subject sequence, is defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul *et al.*, J. Mol. Biol. (1997) 215:403-410) with all the search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A % identity value is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is

being reported. "Percent (%) amino acid sequence similarity" is determined by doing the same calculation as for determining % amino acid sequence identity, but including conservative amino acid substitutions in addition to identical amino acids in the computation.

- 5 A conservative amino acid substitution is one in which an amino acid is substituted for another amino acid having similar properties such that the folding or activity of the protein is not significantly affected. Aromatic amino acids that can be substituted for each other are phenylalanine, tryptophan, and tyrosine; interchangeable hydrophobic amino acids are leucine, isoleucine, methionine, and valine; interchangeable polar amino acids are glutamine and asparagine; interchangeable basic amino acids are arginine, lysine and
10 histidine; interchangeable acidic amino acids are aspartic acid and glutamic acid; and interchangeable small amino acids are alanine, serine, threonine, cysteine and glycine.

- Alternatively, an alignment for nucleic acid sequences is provided by the local homology algorithm of Smith and Waterman (Smith and Waterman, 1981, Advances in
15 Applied Mathematics 2:482-489; database: European Bioinformatics Institute; Smith and Waterman, 1981, J. of Molec.Biol., 147:195-197; Nicholas et al., 1998, "A Tutorial on Searching Sequence Databases and Sequence Scoring Methods" (www.psc.edu) and references cited therein.; W.R. Pearson, 1991, Genomics 11:635-650). This algorithm can be applied to amino acid sequences by using the scoring matrix developed by Dayhoff
20 (Dayhoff: Atlas of Protein Sequences and Structure, M. O. Dayhoff ed., 5 suppl. 3:353-358, National Biomedical Research Foundation, Washington, D.C., USA), and normalized by Gribskov (Gribskov 1986 Nucl. Acids Res. 14(6):6745-6763). The Smith-Waterman algorithm may be employed where default parameters are used for scoring (for example, gap open penalty of 12, gap extension penalty of two). From the data generated, the
25 "Match" value reflects "sequence identity."

- Derivative nucleic acid molecules of the subject nucleic acid molecules include sequences that hybridize to the nucleic acid sequence of any of SEQ ID NOs:1-56. The stringency of hybridization can be controlled by temperature, ionic strength, pH, and the presence of denaturing agents such as formamide during hybridization and washing.
30 Conditions routinely used are set out in readily available procedure texts (e.g., Current Protocol in Molecular Biology, Vol. 1, Chap. 2.10, John Wiley & Sons, Publishers (1994); Sambrook *et al.*, Molecular Cloning, Cold Spring Harbor (1989)). In some embodiments, a nucleic acid molecule of the invention is capable of hybridizing to a nucleic acid molecule containing the nucleotide sequence of any one of SEQ ID NOs:1-56 under high

stringency hybridization conditions that are: prehybridization of filters containing nucleic acid for 8 hours to overnight at 65° C in a solution comprising 6X single strength citrate (SSC) (1X SSC is 0.15 M NaCl, 0.015 M Na citrate; pH 7.0), 5X Denhardt's solution, 0.05% sodium pyrophosphate and 100 µg/ml herring sperm DNA; hybridization for 18-20
5 hours at 65° C in a solution containing 6X SSC, 1X Denhardt's solution, 100 µg/ml yeast tRNA and 0.05% sodium pyrophosphate; and washing of filters at 65° C for 1h in a solution containing 0.1X SSC and 0.1% SDS (sodium dodecyl sulfate).

In other embodiments, moderately stringent hybridization conditions are used that are: pretreatment of filters containing nucleic acid for 6 h at 40° C in a solution containing
10 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.1% PVP, 0.1% Ficoll, 1% BSA, and 500 µg/ml denatured salmon sperm DNA; hybridization for 18-20h at 40° C in a solution containing 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 µg/ml salmon sperm DNA, and 10% (wt/vol) dextran sulfate; followed by washing twice for 1 hour at 55° C in a solution
15 containing 2X SSC and 0.1% SDS.

Alternatively, low stringency conditions can be used that are: incubation for 8 hours to overnight at 37° C in a solution comprising 20% formamide, 5 x SSC, 50 mM sodium phosphate (pH 7.6), 5X Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured sheared salmon sperm DNA; hybridization in the same buffer for 18 to 20
20 hours; and washing of filters in 1 x SSC at about 37° C for 1 hour.

Isolation, Production, Expression, and Mis-expression of MP53 Nucleic Acids and Polypeptides

MP53 nucleic acids and polypeptides, useful for identifying and testing agents that
25 modulate MP53 function and for other applications related to the involvement of MP53 in the p53 pathway. MP53 nucleic acids and derivatives and orthologs thereof may be obtained using any available method. For instance, techniques for isolating cDNA or genomic DNA sequences of interest by screening DNA libraries or by using polymerase chain reaction (PCR) are well known in the art. In general, the particular use for the
30 protein will dictate the particulars of expression, production, and purification methods. For instance, production of proteins for use in screening for modulating agents may require methods that preserve specific biological activities of these proteins, whereas production of proteins for antibody generation may require structural integrity of particular epitopes. Expression of proteins to be purified for screening or antibody production may

require the addition of specific tags (*e.g.*, generation of fusion proteins). Overexpression of an MP53 protein for assays used to assess MP53 function, such as involvement in cell cycle regulation or hypoxic response, may require expression in eukaryotic cell lines capable of these cellular activities. Techniques for the expression, production, and purification of proteins are well known in the art; any suitable means therefore may be used (*e.g.*, Higgins SJ and Hames BD (eds.) *Protein Expression: A Practical Approach*, Oxford University Press Inc., New York 1999; Stanbury PF et al., *Principles of Fermentation Technology*, 2nd edition, Elsevier Science, New York, 1995; Doonan S (ed.) *Protein Purification Protocols*, Humana Press, New Jersey, 1996; Coligan JE et al, *Current Protocols in Protein Science* (eds.), 1999, John Wiley & Sons, New York). In particular embodiments, recombinant MP53 is expressed in a cell line known to have defective p53 function (*e.g.* SAOS-2 osteoblasts, H1299 lung cancer cells, C33A and HT3 cervical cancer cells, HT-29 and DLD-1 colon cancer cells, among others, available from American Type Culture Collection (ATCC), Manassas, VA). The recombinant cells are used in cell-based screening assay systems of the invention, as described further below.

The nucleotide sequence encoding an MP53 polypeptide can be inserted into any appropriate expression vector. The necessary transcriptional and translational signals, including promoter/enhancer element, can derive from the native MP53 gene and/or its flanking regions or can be heterologous. A variety of host-vector expression systems may be utilized, such as mammalian cell systems infected with virus (*e.g.* vaccinia virus, adenovirus, *etc.*); insect cell systems infected with virus (*e.g.* baculovirus); microorganisms such as yeast containing yeast vectors, or bacteria transformed with bacteriophage, plasmid, or cosmid DNA. An isolated host cell strain that modulates the expression of, modifies, and/or specifically processes the gene product may be used.

To detect expression of the MP53 gene product, the expression vector can comprise a promoter operably linked to an MP53 gene nucleic acid, one or more origins of replication, and, one or more selectable markers (*e.g.* thymidine kinase activity, resistance to antibiotics, *etc.*). Alternatively, recombinant expression vectors can be identified by assaying for the expression of the MP53 gene product based on the physical or functional properties of the MP53 protein in *in vitro* assay systems (*e.g.* immunoassays).

The MP53 protein, fragment, or derivative may be optionally expressed as a fusion, or chimeric protein product (*i.e.* it is joined via a peptide bond to a heterologous protein sequence of a different protein), for example to facilitate purification or detection. A chimeric product can be made by ligating the appropriate nucleic acid sequences

encoding the desired amino acid sequences to each other using standard methods and expressing the chimeric product. A chimeric product may also be made by protein synthetic techniques, *e.g.* by use of a peptide synthesizer (Hunkapiller *et al.*, Nature (1984) 310:105-111).

- 5 Once a recombinant cell that expresses the MP53 gene sequence is identified, the gene product can be isolated and purified using standard methods (*e.g.* ion exchange, affinity, and gel exclusion chromatography; centrifugation; differential solubility; electrophoresis). Alternatively, native MP53 proteins can be purified from natural
10 sources, by standard methods (*e.g.* immunoaffinity purification). Once a protein is obtained, it may be quantified and its activity measured by appropriate methods, such as immunoassay, bioassay, or other measurements of physical properties, such as crystallography.

- The methods of this invention may also use cells that have been engineered for altered expression (mis-expression) of MP53 or other genes associated with the p53
15 pathway. As used herein, mis-expression encompasses ectopic expression, over-expression, under-expression, and non-expression (*e.g.* by gene knock-out or blocking expression that would otherwise normally occur).

Genetically modified animals

- 20 Animal models that have been genetically modified to alter MP53 expression may be used in *in vivo* assays to test for activity of a candidate p53 modulating agent, or to further assess the role of MP53 in a p53 pathway process such as apoptosis or cell proliferation. Preferably, the altered MP53 expression results in a detectable phenotype, such as decreased or increased levels of cell proliferation, angiogenesis, or apoptosis
25 compared to control animals having normal MP53 expression. The genetically modified animal may additionally have altered p53 expression (*e.g.* p53 knockout). Preferred genetically modified animals are mammals such as primates, rodents (preferably mice or rats), among others. Preferred non-mammalian species include zebrafish, *C. elegans*, and *Drosophila*. Preferred genetically modified animals are transgenic animals having a
30 heterologous nucleic acid sequence present as an extrachromosomal element in a portion of its cells, *i.e.* mosaic animals (see, for example, techniques described by Jakobovits, 1994, Curr. Biol. 4:761-763.) or stably integrated into its germ line DNA (*i.e.*, in the genomic sequence of most or all of its cells). Heterologous nucleic acid is introduced into

the germ line of such transgenic animals by genetic manipulation of, for example, embryos or embryonic stem cells of the host animal.

Methods of making transgenic animals are well-known in the art (for transgenic mice see Brinster et al., Proc. Nat. Acad. Sci. USA 82: 4438-4442 (1985), U.S. Pat. Nos. 4,736,866 and 4,870,009, both by Leder et al., U.S. Pat. No. 4,873,191 by Wagner et al., and Hogan, B., Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986); for particle bombardment see U.S. Pat. No., 4,945,050, by Sandford *et al.*; for transgenic *Drosophila* see Rubin and Spradling, Science (1982) 218:348-53 and U.S. Pat. No. 4,670,388; for transgenic insects see Berghammer A.J. *et al.*, A Universal Marker for Transgenic Insects (1999) Nature 402:370-371; for transgenic Zebrafish see Lin S., Transgenic Zebrafish, Methods Mol Biol. (2000);136:375-3830); for microinjection procedures for fish, amphibian eggs and birds see Houdebine and Chourrout, Experientia (1991) 47:897-905; for transgenic rats see Hammer *et al.*, Cell (1990) 63:1099-1112; and for culturing of embryonic stem (ES) cells and the subsequent production of transgenic animals by the introduction of DNA into ES cells using methods such as electroporation, calcium phosphate/DNA precipitation and direct injection see, e.g., Teratocarcinomas and Embryonic Stem Cells, A Practical Approach, E. J. Robertson, ed., IRL Press (1987)). Clones of the nonhuman transgenic animals can be produced according to available methods (see Wilmut, I. *et al.* (1997) Nature 385:810-813; and PCT International Publication Nos. WO 97/07668 and WO 97/07669).

In one embodiment, the transgenic animal is a "knock-out" animal having a heterozygous or homozygous alteration in the sequence of an endogenous MP53 gene that results in a decrease of MP53 function, preferably such that MP53 expression is undetectable or insignificant. Knock-out animals are typically generated by homologous recombination with a vector comprising a transgene having at least a portion of the gene to be knocked out. Typically a deletion, addition or substitution has been introduced into the transgene to functionally disrupt it. The transgene can be a human gene (e.g., from a human genomic clone) but more preferably is an ortholog of the human gene derived from the transgenic host species. For example, a mouse MP53 gene is used to construct a homologous recombination vector suitable for altering an endogenous MP53 gene in the mouse genome. Detailed methodologies for homologous recombination in mice are available (see Capecchi, Science (1989) 244:1288-1292; Joyner *et al.*, Nature (1989) 338:153-156). Procedures for the production of non-rodent transgenic mammals and other animals are also available (Houdebine and Chourrout, *supra*; Pursel *et al.*, Science (1989)

244:1281-1288; Simms *et al.*, Bio/Technology (1988) 6:179-183). In a preferred embodiment, knock-out animals, such as mice harboring a knockout of a specific gene, may be used to produce antibodies against the human counterpart of the gene that has been knocked out (Claesson MH *et al.*, (1994) Scan J Immunol 40:257-264; Declerck PJ *et al.*, (1995) J Biol Chem. 270:8397-400).

In another embodiment, the transgenic animal is a "knock-in" animal having an alteration in its genome that results in altered expression (e.g., increased (including ectopic) or decreased expression) of the MP53 gene, e.g., by introduction of additional copies of MP53, or by operatively inserting a regulatory sequence that provides for altered expression of an endogenous copy of the MP53 gene. Such regulatory sequences include inducible, tissue-specific, and constitutive promoters and enhancer elements. The knock-in can be homozygous or heterozygous.

Transgenic nonhuman animals can also be produced that contain selected systems allowing for regulated expression of the transgene. One example of such a system that may be produced is the cre/loxP recombinase system of bacteriophage P1 (Lakso *et al.*, PNAS (1992) 89:6232-6236; U.S. Pat. No. 4,959,317). If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.* (1991) Science 251:1351-1355; U.S. Pat. No. 5,654,182). In a preferred embodiment, both Cre-LoxP and Flp-Frt are used in the same system to regulate expression of the transgene, and for sequential deletion of vector sequences in the same cell (Sun X *et al.* (2000) Nat Genet 25:83-6).

The genetically modified animals can be used in genetic studies to further elucidate the p53 pathway, as animal models of disease and disorders implicating defective p53 function, and for *in vivo* testing of candidate therapeutic agents, such as those identified in screens described below. The candidate therapeutic agents are administered to a genetically modified animal having altered MP53 function and phenotypic changes are compared with appropriate control animals such as genetically modified animals that receive placebo treatment, and/or animals with unaltered MP53 expression that receive candidate therapeutic agent.

In addition to the above-described genetically modified animals having altered MP53 function, animal models having defective p53 function (and otherwise normal MP53 function), can be used in the methods of the present invention. For example, a p53 knockout mouse can be used to assess, *in vivo*, the activity of a candidate p53 modulating agent identified in one of the *in vitro* assays described below. p53 knockout mice are described in the literature (Jacks et al., Nature 2001;410:1111-1116, 1043-1044; Donehower *et al.*, supra). Preferably, the candidate p53 modulating agent when administered to a model system with cells defective in p53 function, produces a detectable phenotypic change in the model system indicating that the p53 function is restored, i.e., the cells exhibit normal cell cycle progression.

Modulating Agents

The invention provides methods to identify agents that interact with and/or modulate the function of MP53 and/or the p53 pathway. Modulating agents identified by the methods are also part of the invention. Such agents are useful in a variety of diagnostic and therapeutic applications associated with the p53 pathway, as well as in further analysis of the MP53 protein and its contribution to the p53 pathway. Accordingly, the invention also provides methods for modulating the p53 pathway comprising the step of specifically modulating MP53 activity by administering a MP53-interacting or -modulating agent.

As used herein, an "MP53-modulating agent" is any agent that modulates MP53 function, for example, an agent that interacts with MP53 to inhibit or enhance MP53 activity or otherwise affect normal MP53 function. MP53 function can be affected at any level, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In a preferred embodiment, the MP53 - modulating agent specifically modulates the function of the MP53. The phrases "specific modulating agent", "specifically modulates", etc., are used herein to refer to modulating agents that directly bind to the MP53 polypeptide or nucleic acid, and preferably inhibit, enhance, or otherwise alter, the function of the MP53. These phrases also encompass modulating agents that alter the interaction of the MP53 with a binding partner, substrate, or cofactor (e.g. by binding to a binding partner of an MP53, or to a protein/binding partner complex, and altering MP53 function). In a further preferred embodiment, the MP53- modulating agent is a modulator of the p53 pathway (e.g. it restores and/or upregulates p53 function) and thus is also a p53-modulating agent.

Preferred MP53-modulating agents include small molecule compounds; MP53-interacting proteins, including antibodies and other biotherapeutics; and nucleic acid modulators such as antisense and RNA inhibitors. The modulating agents may be formulated in pharmaceutical compositions, for example, as compositions that may
5 comprise other active ingredients, as in combination therapy, and/or suitable carriers or excipients. Techniques for formulation and administration of the compounds may be found in "Remington's Pharmaceutical Sciences" Mack Publishing Co., Easton, PA, 19th edition.

10 **Small molecule modulators**

Small molecules are often preferred to modulate function of proteins with enzymatic function, and/or containing protein interaction domains. Chemical agents, referred to in the art as "small molecule" compounds are typically organic, non-peptide molecules, having a molecular weight less than 10,000, preferably less than 5,000, more
15 preferably less than 1,000, and most preferably less than 500. This class of modulators includes chemically synthesized molecules, for instance, compounds from combinatorial chemical libraries. Synthetic compounds may be rationally designed or identified based on known or inferred properties of the MP53 protein or may be identified by screening compound libraries. Alternative appropriate modulators of this class are natural products,
20 particularly secondary metabolites from organisms such as plants or fungi, which can also be identified by screening compound libraries for MP53-modulating activity. Methods for generating and obtaining compounds are well known in the art (Schreiber SL, Science (2000) 151: 1964-1969; Radmann J and Gunther J, Science (2000) 151:1947-1948).

Small molecule modulators identified from screening assays, as described below,
25 can be used as lead compounds from which candidate clinical compounds may be designed, optimized, and synthesized. Such clinical compounds may have utility in treating pathologies associated with the p53 pathway. The activity of candidate small molecule modulating agents may be improved several-fold through iterative secondary functional validation, as further described below, structure determination, and candidate
30 modulator modification and testing. Additionally, candidate clinical compounds are generated with specific regard to clinical and pharmacological properties. For example, the reagents may be derivatized and re-screened using *in vitro* and *in vivo* assays to optimize activity and minimize toxicity for pharmaceutical development.

Protein Modulators

Specific MP53-interacting proteins are useful in a variety of diagnostic and therapeutic applications related to the p53 pathway and related disorders, as well as in validation assays for other MP53-modulating agents. In a preferred embodiment, MP53-interacting proteins affect normal MP53 function, including transcription, protein
 5 expression, protein localization, and cellular or extra-cellular activity. In another embodiment, MP53-interacting proteins are useful in detecting and providing information about the function of MP53 proteins, as is relevant to p53 related disorders, such as cancer (e.g., for diagnostic means).

10 An MP53-interacting protein may be endogenous, i.e. one that naturally interacts genetically or biochemically with an MP53, such as a member of the MP53 pathway that modulates MP53 expression, localization, and/or activity. MP53-modulators include dominant negative forms of MP53-interacting proteins and of MP53 proteins themselves. Yeast two-hybrid and variant screens offer preferred methods for identifying endogenous
 15 MP53-interacting proteins (Finley, R. L. et al. (1996) in DNA Cloning-Expression Systems: A Practical Approach, eds. Glover D. & Hames B. D (Oxford University Press, Oxford, England), pp. 169-203; Fashema SF et al., Gene (2000) 250:1-14; Drees BL Curr Opin Chem Biol (1999) 3:64-70; Vidal M and Legrain P Nucleic Acids Res (1999) 27:919-29; and U.S. Pat. No. 5,928,868). Mass spectrometry is an alternative preferred
 20 method for the elucidation of protein complexes (reviewed in, e.g., Pandley A and Mann M, Nature (2000) 405:837-846; Yates JR 3rd, Trends Genet (2000) 16:5-8).

An MP53-interacting protein may be an exogenous protein, such as an MP53-specific antibody or a T-cell antigen receptor (see, e.g., Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory; Harlow and Lane
 25 (1999) Using antibodies: a laboratory manual. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press). MP53 antibodies are further discussed below.

In preferred embodiments, an MP53-interacting protein specifically binds an MP53 protein. In alternative preferred embodiments, an MP53-modulating agent binds an MP53 substrate, binding partner, or cofactor.

30

Antibodies

In another embodiment, the protein modulator is an MP53 specific antibody agonist or antagonist. The antibodies have therapeutic and diagnostic utilities, and can be used in screening assays to identify MP53 modulators. The antibodies can also be used in

dissecting the portions of the MP53 pathway responsible for various cellular responses and in the general processing and maturation of the MP53.

Antibodies that specifically bind MP53 polypeptides can be generated using known methods. Preferably the antibody is specific to a mammalian ortholog of MP53 polypeptide, and more preferably, to human MP53. Antibodies may be polyclonal, 5 monoclonal (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab')₂ fragments, fragments produced by a FAb expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above. Epitopes of MP53 which are particularly antigenic can be selected, for example, by routine 10 screening of MP53 polypeptides for antigenicity or by applying a theoretical method for selecting antigenic regions of a protein (Hopp and Wood (1981), Proc. Natl. Acad. Sci. U.S.A. 78:3824-28; Hopp and Wood, (1983) Mol. Immunol. 20:483-89; Sutcliffe et al., (1983) Science 219:660-66) to the amino acid sequence of any of SEQ ID NOs:57-112. Monoclonal antibodies with affinities of 10^8 M^{-1} preferably 10^9 M^{-1} to 10^{10} M^{-1} , or 15 stronger can be made by standard procedures as described (Harlow and Lane, *supra*; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed) Academic Press, New York; and U.S. Pat. Nos. 4,381,292; 4,451,570; and 4,618,577). Antibodies may be generated against crude cell extracts of MP53 or substantially purified fragments thereof. If MP53 fragments are used, they preferably comprise at least 10, and more preferably, at 20 least 20 contiguous amino acids of an MP53 protein. In a particular embodiment, MP53-specific antigens and/or immunogens are coupled to carrier proteins that stimulate the immune response. For example, the subject polypeptides are covalently coupled to the keyhole limpet hemocyanin (KLH) carrier, and the conjugate is emulsified in Freund's complete adjuvant, which enhances the immune response. An appropriate immune system 25 such as a laboratory rabbit or mouse is immunized according to conventional protocols.

The presence of MP53-specific antibodies is assayed by an appropriate assay such as a solid phase enzyme-linked immunosorbent assay (ELISA) using immobilized corresponding MP53 polypeptides. Other assays, such as radioimmunoassays or fluorescent assays might also be used.

30 Chimeric antibodies specific to MP53 polypeptides can be made that contain different portions from different animal species. For instance, a human immunoglobulin constant region may be linked to a variable region of a murine mAb, such that the antibody derives its biological activity from the human antibody, and its binding specificity from the murine fragment. Chimeric antibodies are produced by splicing

together genes that encode the appropriate regions from each species (Morrison et al., Proc. Natl. Acad. Sci. (1984) 81:6851-6855; Neuberger et al., Nature (1984) 312:604-608; Takeda et al., Nature (1985) 31:452-454). Humanized antibodies, which are a form of chimeric antibodies, can be generated by grafting complementary-determining regions (CDRs) (Carlos, T. M., J. M. Harlan. 1994. Blood 84:2068-2101) of mouse antibodies into a background of human framework regions and constant regions by recombinant DNA technology (Riechmann LM, et al., 1988 Nature 323: 323-327). Humanized antibodies contain ~10% murine sequences and ~90% human sequences, and thus further reduce or eliminate immunogenicity, while retaining the antibody specificities (Co MS, and Queen C. 1991 Nature 351: 501-501; Morrison SL. 1992 Ann. Rev. Immun. 10:239-265). Humanized antibodies and methods of their production are well-known in the art (U.S. Pat. Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370).

MP53-specific single chain antibodies which are recombinant, single chain polypeptides formed by linking the heavy and light chain fragments of the Fv regions via an amino acid bridge, can be produced by methods known in the art (U.S. Pat. No. 4,946,778; Bird, Science (1988) 242:423-426; Huston et al., Proc. Natl. Acad. Sci. USA (1988) 85:5879-5883; and Ward et al., Nature (1989) 334:544-546).

Other suitable techniques for antibody production involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors (Huse et al., Science (1989) 246:1275-1281). As used herein, T-cell antigen receptors are included within the scope of antibody modulators (Harlow and Lane, 1988, *supra*).

The polypeptides and antibodies of the present invention may be used with or without modification. Frequently, antibodies will be labeled by joining, either covalently or non-covalently, a substance that provides for a detectable signal, or that is toxic to cells that express the targeted protein (Menard S, et al., Int J. Biol Markers (1989) 4:131-134). A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, fluorescent emitting lanthanide metals, chemiluminescent moieties, bioluminescent moieties, magnetic particles, and the like (U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241). Also, recombinant immunoglobulins may be produced (U.S. Pat. No. 4,816,567). Antibodies to cytoplasmic polypeptides may

be delivered and reach their targets by conjugation with membrane-penetrating toxin proteins (U.S. Pat. No. 6,086,900).

When used therapeutically in a patient, the antibodies of the subject invention are typically administered parenterally, when possible at the target site, or intravenously. The therapeutically effective dose and dosage regimen is determined by clinical studies. Typically, the amount of antibody administered is in the range of about 0.1 mg/kg –to about 10 mg/kg of patient weight. For parenteral administration, the antibodies are formulated in a unit dosage injectable form (e.g., solution, suspension, emulsion) in association with a pharmaceutically acceptable vehicle. Such vehicles are inherently nontoxic and non-therapeutic. Examples are water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Nonaqueous vehicles such as fixed oils, ethyl oleate, or liposome carriers may also be used. The vehicle may contain minor amounts of additives, such as buffers and preservatives, which enhance isotonicity and chemical stability or otherwise enhance therapeutic potential. The antibodies' concentrations in such vehicles are typically in the range of about 1 mg/ml to about 10 mg/ml. Immunotherapeutic methods are further described in the literature (US Pat. No. 5,859,206; WO0073469).

Specific biotherapeutics

In a preferred embodiment, an MP53-interacting protein may have biotherapeutic applications. Biotherapeutic agents formulated in pharmaceutically acceptable carriers and dosages may be used to activate or inhibit signal transduction pathways. This modulation may be accomplished by binding a ligand, thus inhibiting the activity of the pathway; or by binding a receptor, either to inhibit activation of, or to activate, the receptor. Alternatively, the biotherapeutic may itself be a ligand capable of activating or inhibiting a receptor. Biotherapeutic agents and methods of producing them are described in detail in U.S. Pat. No. 6,146,628.

When the MP53 is a ligand, it may be used as a biotherapeutic agent to activate or inhibit its natural receptor. Alternatively, antibodies against MP53, as described in the previous section, may be used as biotherapeutic agents.

When the MP53 is a receptor, its ligand(s), antibodies to the ligand(s) or the MP53 itself may be used as biotherapeutics to modulate the activity of MP53 in the p53 pathway.

Nucleic Acid Modulators

Other preferred MP53-modulating agents comprise nucleic acid molecules, such as antisense oligomers or double stranded RNA (dsRNA), which generally inhibit MP53 activity. Preferred nucleic acid modulators interfere with the function of the MP53 nucleic acid such as DNA replication, transcription, translocation of the MP53 RNA to the site of protein translation, translation of protein from the MP53 RNA, splicing of the MP53 RNA to yield one or more mRNA species, or catalytic activity which may be engaged in or facilitated by the MP53 RNA.

In one embodiment, the antisense oligomer is an oligonucleotide that is sufficiently complementary to an MP53 mRNA to bind to and prevent translation, preferably by binding to the 5' untranslated region. MP53-specific antisense oligonucleotides, preferably range from at least 6 to about 200 nucleotides. In some embodiments the oligonucleotide is preferably at least 10, 15, or 20 nucleotides in length. In other embodiments, the oligonucleotide is preferably less than 50, 40, or 30 nucleotides in length. The oligonucleotide can be DNA or RNA or a chimeric mixture or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone. The oligonucleotide may include other appending groups such as peptides, agents that facilitate transport across the cell membrane, hybridization-triggered cleavage agents, and intercalating agents.

In another embodiment, the antisense oligomer is a phosphothioate morpholino oligomer (PMO). PMOs are assembled from four different morpholino subunits, each of which contain one of four genetic bases (A, C, G, or T) linked to a six-membered morpholine ring. Polymers of these subunits are joined by non-ionic phosphodiamidate intersubunit linkages. Details of how to make and use PMOs and other antisense oligomers are well known in the art (e.g. see WO99/18193; Probst JC, Antisense Oligodeoxynucleotide and Ribozyme Design, Methods. (2000) 22(3):271-281; Summerton J, and Weller D. 1997 Antisense Nucleic Acid Drug Dev. :7:187-95; US Pat. No. 5,235,033; and US Pat No. 5,378,841).

Alternative preferred MP53 nucleic acid modulators are double-stranded RNA species mediating RNA interference (RNAi). RNAi is the process of sequence-specific, post-transcriptional gene silencing in animals and plants, initiated by double-stranded RNA (dsRNA) that is homologous in sequence to the silenced gene. Methods relating to the use of RNAi to silence genes in *C. elegans*, *Drosophila*, plants, and humans are known

in the art (Fire A, et al., 1998 Nature 391:806-811; Fire, A. Trends Genet. 15, 358-363 (1999); Sharp, P. A. RNA interference 2001. Genes Dev. 15, 485-490 (2001); Hammond, S. M., et al., Nature Rev. Genet. 2, 110-1119 (2001); Tuschl, T. Chem. Biochem. 2, 239-245 (2001); Hamilton, A. et al., Science 286, 950-952 (1999); Hammond, S. M., et al.,
5 Nature 404, 293-296 (2000); Zamore, P. D., et al., Cell 101, 25-33 (2000); Bernstein, E., et al., Nature 409, 363-366 (2001); Elbashir, S. M., et al., Genes Dev. 15, 188-200 (2001); WO0129058; WO9932619; Elbashir SM, et al., 2001 Nature 411:494-498).

Nucleic acid modulators are commonly used as research reagents, diagnostics, and therapeutics. For example, antisense oligonucleotides, which are able to inhibit gene
10 expression with exquisite specificity, are often used to elucidate the function of particular genes (see, for example, U.S. Pat. No. 6,165,790). Nucleic acid modulators are also used, for example, to distinguish between functions of various members of a biological pathway. For example, antisense oligomers have been employed as therapeutic moieties in the treatment of disease states in animals and man and have been demonstrated in numerous
15 clinical trials to be safe and effective (Milligan JF, *et al*, Current Concepts in Antisense Drug Design, J Med Chem. (1993) 36:1923-1937; Tonkinson JL *et al.*, Antisense Oligodeoxynucleotides as Clinical Therapeutic Agents, Cancer Invest. (1996) 14:54-65). Accordingly, in one aspect of the invention, an MP53-specific nucleic acid modulator is used in an assay to further elucidate the role of the MP53 in the p53 pathway, and/or its
20 relationship to other members of the pathway. In another aspect of the invention, an MP53-specific antisense oligomer is used as a therapeutic agent for treatment of p53-related disease states.

Assay Systems

25 The invention provides assay systems and screening methods for identifying specific modulators of MP53 activity. As used herein, an "assay system" encompasses all the components required for performing and analyzing results of an assay that detects and/or measures a particular event. In general, primary assays are used to identify or confirm a modulator's specific biochemical or molecular effect with respect to the MP53
30 nucleic acid or protein. In general, secondary assays further assess the activity of a MP53 modulating agent identified by a primary assay and may confirm that the modulating agent affects MP53 in a manner relevant to the p53 pathway. In some cases, MP53 modulators will be directly tested in a secondary assay.

In a preferred embodiment, the screening method comprises contacting a suitable assay system comprising an MP53 polypeptide or nucleic acid with a candidate agent under conditions whereby, but for the presence of the agent, the system provides a reference activity (e.g. binding activity), which is based on the particular molecular event the screening method detects. A statistically significant difference between the agent-biased activity and the reference activity indicates that the candidate agent modulates MP53 activity, and hence the p53 pathway. The MP53 polypeptide or nucleic acid used in the assay may comprise any of the nucleic acids or polypeptides described above.

Primary Assays

The type of modulator tested generally determines the type of primary assay.

Primary assays for small molecule modulators

For small molecule modulators, screening assays are used to identify candidate modulators. Screening assays may be cell-based or may use a cell-free system that recreates or retains the relevant biochemical reaction of the target protein (reviewed in Sittampalam GS *et al.*, Curr Opin Chem Biol (1997) 1:384-91 and accompanying references). As used herein the term "cell-based" refers to assays using live cells, dead cells, or a particular cellular fraction, such as a membrane, endoplasmic reticulum, or mitochondrial fraction. The term "cell free" encompasses assays using substantially purified protein (either endogenous or recombinantly produced), partially purified or crude cellular extracts. Screening assays may detect a variety of molecular events, including protein-DNA interactions, protein-protein interactions (e.g., receptor-ligand binding), transcriptional activity (e.g., using a reporter gene), enzymatic activity (e.g., via a property of the substrate), activity of second messengers, immunogenicity and changes in cellular morphology or other cellular characteristics. Appropriate screening assays may use a wide range of detection methods including fluorescent, radioactive, colorimetric, spectrophotometric, and amperometric methods, to provide a read-out for the particular molecular event detected.

Cell-based screening assays usually require systems for recombinant expression of MP53 and any auxiliary proteins demanded by the particular assay. Appropriate methods for generating recombinant proteins produce sufficient quantities of proteins that retain their relevant biological activities and are of sufficient purity to optimize activity and assure assay reproducibility. Yeast two-hybrid and variant screens, and mass spectrometry

provide preferred methods for determining protein-protein interactions and elucidation of protein complexes. In certain applications, when MP53-interacting proteins are used in screens to identify small molecule modulators, the binding specificity of the interacting protein to the MP53 protein may be assayed by various known methods such as substrate processing (e.g. ability of the candidate MP53-specific binding agents to function as negative effectors in MP53-expressing cells), binding equilibrium constants (usually at least about 10^7 M^{-1} , preferably at least about 10^8 M^{-1} , more preferably at least about 10^9 M^{-1}), and immunogenicity (e.g. ability to elicit MP53 specific antibody in a heterologous host such as a mouse, rat, goat or rabbit). For enzymes and receptors, binding may be assayed by, respectively, substrate and ligand processing.

The screening assay may measure a candidate agent's ability to specifically bind to or modulate activity of a MP53 polypeptide, a fusion protein thereof, or to cells or membranes bearing the polypeptide or fusion protein. The MP53 polypeptide can be full length or a fragment thereof that retains functional MP53 activity. The MP53 polypeptide may be fused to another polypeptide, such as a peptide tag for detection or anchoring, or to another tag. The MP53 polypeptide is preferably human MP53, or is an ortholog or derivative thereof as described above. In a preferred embodiment, the screening assay detects candidate agent-based modulation of MP53 interaction with a binding target, such as an endogenous or exogenous protein or other substrate that has MP53-specific binding activity, and can be used to assess normal MP53 gene function.

Suitable assay formats that may be adapted to screen for MP53 modulators are known in the art. Preferred screening assays are high throughput or ultra high throughput and thus provide automated, cost-effective means of screening compound libraries for lead compounds (Fernandes PB, Curr Opin Chem Biol (1998) 2:597-603; Sundberg SA, Curr Opin Biotechnol 2000, 11:47-53). In one preferred embodiment, screening assays uses fluorescence technologies, including fluorescence polarization, time-resolved fluorescence, and fluorescence resonance energy transfer. These systems offer means to monitor protein-protein or DNA-protein interactions in which the intensity of the signal emitted from dye-labeled molecules depends upon their interactions with partner molecules (e.g., Selvin PR, Nat Struct Biol (2000) 7:730-4; Fernandes PB, *supra*; Hertzberg RP and Pope AJ, Curr Opin Chem Biol (2000) 4:445-451).

A variety of suitable assay systems may be used to identify candidate MP53 and p53 pathway modulators (e.g. U.S. Pat. No. 6,165,992 (kinase assays); U.S. Pat. Nos. 5,550,019 and 6,133,437 (apoptosis assays); U.S. Pat. No. 6,020,135 (p53 modulation),

and U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434 (angiogenesis assays), among others). Specific preferred assays are described in more detail below.

Protein kinases, key signal transduction proteins that may be either membrane-associated or intracellular, catalyze the transfer of gamma phosphate from adenosine triphosphate (ATP) to a serine, threonine or tyrosine residue in a protein substrate. Radioassays, which monitor the transfer from [γ - ^{32}P or ^{33}P]ATP, are frequently used to assay kinase activity. For instance, a scintillation assay for p56 (lck) kinase activity monitors the transfer of the gamma phosphate from [γ - ^{33}P] ATP to a biotinylated peptide substrate. The substrate is captured on a streptavidin coated bead that transmits the signal (Beveridge M *et al.*, J Biomol Screen (2000) 5:205-212). This assay uses the scintillation proximity assay (SPA), in which only radio-ligand bound to receptors tethered to the surface of an SPA bead are detected by the scintillant immobilized within it, allowing binding to be measured without separation of bound from free ligand. Other assays for protein kinase activity may use antibodies that specifically recognize phosphorylated substrates. For instance, the kinase receptor activation (KIRA) assay measures receptor tyrosine kinase activity by ligand stimulating the intact receptor in cultured cells, then capturing solubilized receptor with specific antibodies and quantifying phosphorylation via phosphotyrosine ELISA (Sadick MD, Dev Biol Stand (1999) 97:121-133). Another example of antibody based assays for protein kinase activity is TRF (time-resolved fluorometry). This method utilizes europium chelate-labeled anti-phosphotyrosine antibodies to detect phosphate transfer to a polymeric substrate coated onto microtiter plate wells. The amount of phosphorylation is then detected using time-resolved, dissociation-enhanced fluorescence (Braunwalder AF, et al., Anal Biochem 1996 Jul 1;238(2):159-64).

Protein phosphatases catalyze the removal of a gamma phosphate from a serine, threonine or tyrosine residue in a protein substrate. Since phosphatases act in opposition to kinases, appropriate assays measure the same parameters as kinase assays. In one example, the dephosphorylation of a fluorescently labeled peptide substrate allows trypsin cleavage of the substrate, which in turn renders the cleaved substrate significantly more fluorescent (Nishikata M *et al.*, Biochem J (1999) 343:35-391). In another example, fluorescence polarization (FP), a solution-based, homogeneous technique requiring no immobilization or separation of reaction components, is used to develop high throughput screening (HTS) assays for protein phosphatases. This assay uses direct binding of the phosphatase with the target, and increasing concentrations of target- phosphatase increase

the rate of dephosphorylation, leading to a change in polarization (Parker GJ et al., (2000) J Biomol Screen 5:77-88).

Endogenous protease inhibitors may inhibit protease activity. In an example of an assay developed for either proteases or protease inhibitors, a biotinylated substrate is
5 coated on a titer plate and hydrolyzed with the protease; the unhydrolyzed substrate is quantified by reaction with alkaline phosphatase-streptavidin complex and detection of the reaction product. The activity of protease inhibitors correlates with the activity of the alkaline phosphatase indicator enzyme (Gan Z *et al.*, Anal Biochem 1999) 268:151-156).

Fatty acid desaturases catalyze the insertion of double bonds into saturated fatty
10 acid molecules. In one application, radioassays for inhibitors of delta-5 and delta-6 fatty acid desaturase activity use thin layer chromatography to detect conversion of fatty acid substrates (Obukowicz et al., Biochem Pharmacol (1998) 55:1045-1058).

RNA folds into a myriad of tertiary structures that are responsible for its diverse functions in cells. In most instances, RNA is associated with RNA-binding proteins
15 (RBPs) that protect, stabilize, package or transport RNA, mediate RNA interactions with other biomolecules or act catalytically on RNA. The structural information obtained for RNA alone and RNA-protein complexes has elucidated a variety of RNA tertiary structures and diverse modes for RNA-protein interaction. The specific interaction of proteins with highly structured RNAs makes it possible to target unique RNA motifs with
20 small molecules, thus making RNA an interesting target for therapeutic intervention. Assays for RNA binding or processing may be based on homogeneous scintillation proximity (Liu J, et al., Anal Biochem 2001 289:239-245), chemiluminescence (Mazumder A, Nucleic Acids Res 1998 26:1996-2000), gel shift (Stull RA, et al., Antisense Nucleic Acid Drug Dev 1996 6:221-228; U.S. Pat. No: 6004749).

Adapter proteins are involved in a wide range of signaling and other cellular
25 processes and generally facilitate protein-protein or protein-nucleic acid interactions via certain conserved motifs, including PDZ, SH2, SH3, PH, TRAF, WD40, LIM, ankyrin repeat, KH and annexin domains, etc. Assays for adapter protein activity may measure protein binding at the conserved motifs. For instance, exemplary assays for SH2 domain-
30 containing proteins have measured binding using fluorescently labeled peptide substrate and fluorescence polarization or laser-scanning techniques (Lynch BA et al., Anal Biochem 1999, 275:62-73; Zuck P et al., Proc Natl Acad Sci USA 1999, 96: 11122-11127). An alternative SH2 binding assay uses radiolabeled peptide. An assay for protein-protein interaction at the LIM domain has used fluorescently labeled LIM-

containing proteins (FHL2 and FHL3) and the fluorescence resonance energy transfer (FRET) technique (Li HY, J Cell Biochem 2001, 80:293-303).

Transporter proteins carry a range of substrates, including nutrients, ions, amino acids, and drugs, across cell membranes. Assays for modulators of transporters may use
5 labeled substrates. For instance, exemplary high throughput screens to identify compounds that interact with different peptide and anion transporters both use fluorescently labeled substrates; the assay for peptide transport additionally uses multiscreeen filtration plates (Blevitt JM et al., J Biomol Screen 1999, 4:87-91; Cihlar T and Ho ES, Anal Biochem 2000, 283:49-55).

10 Ion channels mediate essential physiological functions, including fluid secretion, electrolyte balance, bioenergetics, and membrane excitability. Assays for channel activity can incorporate ion-sensitive dyes or proteins or voltage-sensitive dyes or proteins, as reviewed in Gonzalez JE *et al.* (Drug Discovery Today (1999) 4:431-439). Alternative methods measure the displacement of known ligands, which may be radio-labeled or
15 fluorescently labeled (*e.g.*, SchMid EL *et al.*, Anal Chem (1998) 70:1331-1338).

Transcription factors control gene transcription. Electrophoretic mobility shift assay (EMSA) or gel shift assay is one of the most powerful methods for studying protein-DNA interactions. High throughput gel shift assays for transcription factors may involve fluorescence (Cyano dye Cy5) labeled oligodeoxynucleotide duplexes as specific probes
20 and an automatic DNA sequencer for analysis (Ruscher K, et al., (2000) J Biotechnol 78:163-70). Alternatively high throughput methods involve colorimetric assays (Renard P, et al. (2001) Nucleic Acids Res 29(4):E21), or homogeneous fluorescence assays for the detection and quantification of sequence-specific DNA-binding proteins (Heyduk T, and Heyduk E (2001) Nat Biotechnol 20:171-6.)

25 Reductases are enzymes of oxidoreductase class that catalyze reactions in which metabolites are reduced. High throughput screening assays for reductases may involve scintillation (Fernandes PB. (1998) Curr Opin Chem Biol 2:597-603; Delaporte E et al. (2001) J Biomol Screen 6:225-231).

Assays for ATPase activity may be performed as described in Blackburn et al
30 (Blackburn CL, et al., (1999) J Org Chem 64:5565-5570). The ATPase assay is performed using the EnzCheck ATPase kit (Molecular Probes). The assays are performed using an Ultraspec spectrophotometer (Pharmacia), and the progress of the reaction are monitored by absorbance increase at 360 nm. Microtubules (1.7 mM final), kinesin (0.11 mM final), inhibitor (or DMSO blank at 5% final), and the EnzCheck components (purine nucleotide

phosphorylase and MESG substrate) are premixed in the cuvette in a reaction buffer (40 mM PIPES pH 6.8, 5 mM paclitaxel, 1 mM EGTA, 5 mM MgCl₂). The reaction is initiated by addition of MgATP (1 mM final).

High throughput assays based on photometric analysis of the activity of decarboxylase enzymes have been described (Breuer M et al (2002) Anal Bioanal Chem 374:1069-73).

High-throughput photometric assays for peroxidases have also been described (Smith AD et al (2001) Int J Vitam Nutr Res 71:87-92; Smith AD and Levander OA (2002) Methods Enzymol 347:113-21).

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Apoptosis assays. Assays for apoptosis may be performed by terminal deoxynucleotidyl transferase-mediated digoxigenin-11-dUTP nick end labeling (TUNEL) assay. The TUNEL assay is used to measure nuclear DNA fragmentation characteristic of apoptosis (Lazebnik *et al.*, 1994, Nature 371, 346), by following the incorporation of fluorescein-dUTP (Yonehara *et al.*, 1989, J. Exp. Med. 169, 1747). Apoptosis may further be assayed by acridine orange staining of tissue culture cells (Lucas, R., et al., 1998, Blood 15:4730-41). An apoptosis assay system may comprise a cell that expresses an MP53, and that optionally has defective p53 function (e.g. p53 is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the apoptosis assay system and changes in induction of apoptosis relative to controls where no test agent is added, identify candidate p53 modulating agents. In some embodiments of the invention, an apoptosis assay may be used as a secondary assay to test a candidate p53 modulating agents that is initially identified using a cell-free assay system. An apoptosis assay may also be used to test whether MP53 function plays a direct role in apoptosis. For example, an apoptosis assay may be performed on cells that over- or under-express MP53 relative to wild type cells. Differences in apoptotic response compared to wild type cells suggests that the MP53 plays a direct role in the apoptotic response. Apoptosis assays are described further in US Pat. No. 6,133,437.

Cell proliferation and cell cycle assays. Cell proliferation may be assayed via bromodeoxyuridine (BRDU) incorporation. This assay identifies a cell population undergoing DNA synthesis by incorporation of BRDU into newly-synthesized DNA. Newly-synthesized DNA may then be detected using an anti-BRDU antibody (Hoshino *et*

al., 1986, *Int. J. Cancer* 38, 369; Campana *et al.*, 1988, *J. Immunol. Meth.* 107, 79), or by other means.

Cell proliferation is also assayed via phospho-histone H3 staining, which identifies a cell population undergoing mitosis by phosphorylation of histone H3. Phosphorylation of histone H3 at serine 10 is detected using an antibody specific to the phosphorylated form of the serine 10 residue of histone H3. (Chadlee, D.N. 1995, *J. Biol. Chem* 270:20098-105). Cell Proliferation may also be examined using [³H]-thymidine incorporation (Chen, J., 1996, *Oncogene* 13:1395-403; Jeoung, J., 1995, *J. Biol. Chem.* 270:18367-73). This assay allows for quantitative characterization of S-phase DNA syntheses. In this assay, cells synthesizing DNA will incorporate [³H]-thymidine into newly synthesized DNA. Incorporation can then be measured by standard techniques such as by counting of radioisotope in a scintillation counter (e.g., Beckman LS 3800 Liquid Scintillation Counter). Another proliferation assay uses the dye Alamar Blue (available from Biosource International), which fluoresces when reduced in living cells and provides an indirect measurement of cell number (Voytik-Harbin SL *et al.*, 1998, *In Vitro Cell Dev Biol Anim* 34:239-46).

Cell proliferation may also be assayed by colony formation in soft agar (Sambrook *et al.*, *Molecular Cloning*, Cold Spring Harbor (1989)). For example, cells transformed with MP53 are seeded in soft agar plates, and colonies are measured and counted after two weeks incubation.

Involvement of a gene in the cell cycle may be assayed by flow cytometry (Gray JW *et al.* (1986) *Int J Radiat Biol Relat Stud Phys Chem Med* 49:237-55). Cells transfected with an MP53 may be stained with propidium iodide and evaluated in a flow cytometer (available from Becton Dickinson), which indicates accumulation of cells in different stages of the cell cycle.

Accordingly, a cell proliferation or cell cycle assay system may comprise a cell that expresses an MP53, and that optionally has defective p53 function (e.g. p53 is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the assay system and changes in cell proliferation or cell cycle relative to controls where no test agent is added, identify candidate p53 modulating agents. In some embodiments of the invention, the cell proliferation or cell cycle assay may be used as a secondary assay to test a candidate p53 modulating agents that is initially identified using another assay system such as a cell-free assay system. A cell proliferation assay may also be used to test whether MP53 function plays a direct role in cell proliferation or cell cycle. For example,

a cell proliferation or cell cycle assay may be performed on cells that over- or under-express MP53 relative to wild type cells. Differences in proliferation or cell cycle compared to wild type cells suggests that the MP53 plays a direct role in cell proliferation or cell cycle.

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Angiogenesis. Angiogenesis may be assayed using various human endothelial cell systems, such as umbilical vein, coronary artery, or dermal cells. Suitable assays include Alamar Blue based assays (available from Biosource International) to measure proliferation; migration assays using fluorescent molecules, such as the use of Becton Dickinson Falcon HTS FluoroBlock cell culture inserts to measure migration of cells through membranes in presence or absence of angiogenesis enhancer or suppressors; and tubule formation assays based on the formation of tubular structures by endothelial cells on Matrigel® (Becton Dickinson). Accordingly, an angiogenesis assay system may comprise a cell that expresses an MP53, and that optionally has defective p53 function (e.g. p53 is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the angiogenesis assay system and changes in angiogenesis relative to controls where no test agent is added, identify candidate p53 modulating agents. In some embodiments of the invention, the angiogenesis assay may be used as a secondary assay to test a candidate p53 modulating agents that is initially identified using another assay system. An angiogenesis assay may also be used to test whether MP53 function plays a direct role in cell proliferation. For example, an angiogenesis assay may be performed on cells that over- or under-express MP53 relative to wild type cells. Differences in angiogenesis compared to wild type cells suggests that the MP53 plays a direct role in angiogenesis. U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434, among others, describe various angiogenesis assays.

Hypoxic induction. The alpha subunit of the transcription factor, hypoxia inducible factor-1 (HIF-1), is upregulated in tumor cells following exposure to hypoxia in vitro. Under hypoxic conditions, HIF-1 stimulates the expression of genes known to be important in tumour cell survival, such as those encoding glycolytic enzymes and VEGF. Induction of such genes by hypoxic conditions may be assayed by growing cells transfected with MP53 in hypoxic conditions (such as with 0.1% O₂, 5% CO₂, and balance N₂, generated in a Napco 7001 incubator (Precision Scientific)) and normoxic conditions, followed by assessment of gene activity or expression by Taqman®. For

example, a hypoxic induction assay system may comprise a cell that expresses an MP53, and that optionally has defective p53 function (e.g. p53 is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the hypoxic induction assay system and changes in hypoxic response relative to controls where no test agent is added, identify candidate p53 modulating agents. In some embodiments of the invention, the hypoxic induction assay may be used as a secondary assay to test a candidate p53 modulating agents that is initially identified using another assay system. A hypoxic induction assay may also be used to test whether MP53 function plays a direct role in the hypoxic response. For example, a hypoxic induction assay may be performed on cells that over- or under-express MP53 relative to wild type cells. Differences in hypoxic response compared to wild type cells suggests that the MP53 plays a direct role in hypoxic induction.

Cell adhesion. Cell adhesion assays measure adhesion of cells to purified adhesion proteins, or adhesion of cells to each other, in presence or absence of candidate modulating agents. Cell-protein adhesion assays measure the ability of agents to modulate the adhesion of cells to purified proteins. For example, recombinant proteins are produced, diluted to 2.5g/mL in PBS, and used to coat the wells of a microtiter plate. The wells used for negative control are not coated. Coated wells are then washed, blocked with 1% BSA, and washed again. Compounds are diluted to 2× final test concentration and added to the blocked, coated wells. Cells are then added to the wells, and the unbound cells are washed off. Retained cells are labeled directly on the plate by adding a membrane-permeable fluorescent dye, such as calcein-AM, and the signal is quantified in a fluorescent microplate reader.

Cell-cell adhesion assays measure the ability of agents to modulate binding of cell adhesion proteins with their native ligands. These assays use cells that naturally or recombinantly express the adhesion protein of choice. In an exemplary assay, cells expressing the cell adhesion protein are plated in wells of a multiwell plate. Cells expressing the ligand are labeled with a membrane-permeable fluorescent dye, such as BCECF, and allowed to adhere to the monolayers in the presence of candidate agents. Unbound cells are washed off, and bound cells are detected using a fluorescence plate reader.

High-throughput cell adhesion assays have also been described. In one such assay, small molecule ligands and peptides are bound to the surface of microscope slides using a

microarray spotter, intact cells are then contacted with the slides, and unbound cells are washed off. In this assay, not only the binding specificity of the peptides and modulators against cell lines are determined, but also the functional cell signaling of attached cells using immunofluorescence techniques in situ on the microchip is measured (Falsey JR et al., Bioconjug Chem. 2001 May-Jun;12(3):346-53).

Tubulogenesis. Tubulogenesis assays monitor the ability of cultured cells, generally endothelial cells, to form tubular structures on a matrix substrate, which generally simulates the environment of the extracellular matrix. Exemplary substrates include MatrigelTM (Becton Dickinson), an extract of basement membrane proteins containing laminin, collagen IV, and heparin sulfate proteoglycan, which is liquid at 4° C and forms a solid gel at 37° C. Other suitable matrices comprise extracellular components such as collagen, fibronectin, and/or fibrin. Cells are stimulated with a pro-angiogenic stimulant, and their ability to form tubules is detected by imaging. Tubules can generally be detected after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Tube formation assays are well known in the art (e.g., Jones MK et al., 1999, Nature Medicine 5:1418-1423). These assays have traditionally involved stimulation with serum or with the growth factors FGF or VEGF. Serum represents an undefined source of growth factors. In a preferred embodiment, the assay is performed with cells cultured in serum free medium, in order to control which process or pathway a candidate agent modulates. Moreover, we have found that different target genes respond differently to stimulation with different pro-angiogenic agents, including inflammatory angiogenic factors such as TNF- α . Thus, in a further preferred embodiment, a tubulogenesis assay system comprises testing an MP53's response to a variety of factors, such as FGF, VEGF, phorbol myristate acetate (PMA), TNF- α , ephrin, etc.

Cell Migration. An invasion/migration assay (also called a migration assay) tests the ability of cells to overcome a physical barrier and to migrate towards pro-angiogenic signals. Migration assays are known in the art (e.g., Paik JH et al., 2001, J Biol Chem 276:11830-11837). In a typical experimental set-up, cultured endothelial cells are seeded onto a matrix-coated porous lamina, with pore sizes generally smaller than typical cell size. The matrix generally simulates the environment of the extracellular matrix, as described above. The lamina is typically a membrane, such as the transwell polycarbonate membrane (Corning Costar Corporation, Cambridge, MA), and is generally part of an

upper chamber that is in fluid contact with a lower chamber containing pro-angiogenic stimuli. Migration is generally assayed after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Migration is assessed as the number of cells that crossed the lamina, and may be detected by staining cells with hemotoxylin solution (VWR Scientific, South San Francisco, CA), or by any other method for determining cell number. In another exemplary set up, cells are fluorescently labeled and migration is detected using fluorescent readings, for instance using the Falcon HTS FluoroBlok (Becton Dickinson). While some migration is observed in the absence of stimulus, migration is greatly increased in response to pro-angiogenic factors. As described above, a preferred assay system for migration/invasion assays comprises testing an MP53's response to a variety of pro-angiogenic factors, including tumor angiogenic and inflammatory angiogenic agents, and culturing the cells in serum free medium.

Sprouting assay. A sprouting assay is a three-dimensional *in vitro* angiogenesis assay that uses a cell-number defined spheroid aggregation of endothelial cells ("spheroid"), embedded in a collagen gel-based matrix. The spheroid can serve as a starting point for the sprouting of capillary-like structures by invasion into the extracellular matrix (termed "cell sprouting") and the subsequent formation of complex anastomosing networks (Korff and Augustin, 1999, J Cell Sci 112:3249-58). In an exemplary experimental set-up, spheroids are prepared by pipetting 400 human umbilical vein endothelial cells into individual wells of a nonadhesive 96-well plates to allow overnight spheroidal aggregation (Korff and Augustin: J Cell Biol 143: 1341-52, 1998). Spheroids are harvested and seeded in 900 μ l of methocel-collagen solution and pipetted into individual wells of a 24 well plate to allow collagen gel polymerization. Test agents are added after 30 min by pipetting 100 μ l of 10-fold concentrated working dilution of the test substances on top of the gel. Plates are incubated at 37°C for 24h. Dishes are fixed at the end of the experimental incubation period by addition of paraformaldehyde. Sprouting intensity of endothelial cells can be quantitated by an automated image analysis system to determine the cumulative sprout length per spheroid.

Primary assays for antibody modulators

For antibody modulators, appropriate primary assays test is a binding assay that tests the antibody's affinity to and specificity for the MP53 protein. Methods for testing antibody affinity and specificity are well known in the art (Harlow and Lane, 1988, 1999,

supra). The enzyme-linked immunosorbant assay (ELISA) is a preferred method for detecting MP53-specific antibodies; others include FACS assays, radioimmunoassays, and fluorescent assays.

In some cases, screening assays described for small molecule modulators may also be used to test antibody modulators.

Primary assays for nucleic acid modulators

For nucleic acid modulators, primary assays may test the ability of the nucleic acid modulator to inhibit or enhance MP53 gene expression, preferably mRNA expression. In general, expression analysis comprises comparing MP53 expression in like populations of cells (*e.g.*, two pools of cells that endogenously or recombinantly express MP53) in the presence and absence of the nucleic acid modulator. Methods for analyzing mRNA and protein expression are well known in the art. For instance, Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR (*e.g.*, using the TaqMan®, PE Applied Biosystems), or microarray analysis may be used to confirm that MP53 mRNA expression is reduced in cells treated with the nucleic acid modulator (*e.g.*, Current Protocols in Molecular Biology (1994) Ausubel FM *et al.*, eds., John Wiley & Sons, Inc., chapter 4; Freeman WM *et al.*, Biotechniques (1999) 26:112-125; Kallioniemi OP, Ann Med 2001, 33:142-147; Blohm DH and Guiseppi-Elie, A Curr Opin Biotechnol 2001, 12:41-47). Protein expression may also be monitored. Proteins are most commonly detected with specific antibodies or antisera directed against either the MP53 protein or specific peptides. A variety of means including Western blotting, ELISA, or in situ detection, are available (Harlow E and Lane D, 1988 and 1999, *supra*).

In some cases, screening assays described for small molecule modulators, particularly in assay systems that involve MP53 mRNA expression, may also be used to test nucleic acid modulators.

Secondary Assays

Secondary assays may be used to further assess the activity of MP53-modulating agent identified by any of the above methods to confirm that the modulating agent affects MP53 in a manner relevant to the p53 pathway. As used herein, MP53-modulating agents encompass candidate clinical compounds or other agents derived from previously identified modulating agent. Secondary assays can also be used to test the activity of a

modulating agent on a particular genetic or biochemical pathway or to test the specificity of the modulating agent's interaction with MP53.

Secondary assays generally compare like populations of cells or animals (*e.g.*, two pools of cells or animals that endogenously or recombinantly express MP53) in the presence and absence of the candidate modulator. In general, such assays test whether treatment of cells or animals with a candidate MP53-modulating agent results in changes in the p53 pathway in comparison to untreated (or mock- or placebo-treated) cells or animals. Certain assays use "sensitized genetic backgrounds", which, as used herein, describe cells or animals engineered for altered expression of genes in the p53 or interacting pathways.

Cell-based assays

Cell based assays may use a variety of mammalian cell lines known to have defective p53 function (*e.g.* SAOS-2 osteoblasts, H1299 lung cancer cells, C33A and HT3 cervical cancer cells, HT-29 and DLD-1 colon cancer cells, among others, available from American Type Culture Collection (ATCC), Manassas, VA). Cell based assays may detect endogenous p53 pathway activity or may rely on recombinant expression of p53 pathway components. Any of the aforementioned assays may be used in this cell-based format. Candidate modulators are typically added to the cell media but may also be injected into cells or delivered by any other efficacious means.

Animal Assays

A variety of non-human animal models of normal or defective p53 pathway may be used to test candidate MP53 modulators. Models for defective p53 pathway typically use genetically modified animals that have been engineered to mis-express (*e.g.*, over-express or lack expression in) genes involved in the p53 pathway. Assays generally require systemic delivery of the candidate modulators, such as by oral administration, injection, etc.

In a preferred embodiment, p53 pathway activity is assessed by monitoring neovascularization and angiogenesis. Animal models with defective and normal p53 are used to test the candidate modulator's affect on MP53 in Matrigel® assays. Matrigel® is an extract of basement membrane proteins, and is composed primarily of laminin, collagen IV, and heparin sulfate proteoglycan. It is provided as a sterile liquid at 4° C, but rapidly forms a solid gel at 37° C. Liquid Matrigel® is mixed with various angiogenic agents,

such as bFGF and VEGF, or with human tumor cells which over-express the MP53. The mixture is then injected subcutaneously(SC) into female athymic nude mice (Taconic, Germantown, NY) to support an intense vascular response. Mice with Matrigel® pellets may be dosed via oral (PO), intraperitoneal (IP), or intravenous (IV) routes with the candidate modulator. Mice are euthanized 5 - 12 days post-injection, and the Matrigel® pellet is harvested for hemoglobin analysis (Sigma plasma hemoglobin kit). Hemoglobin content of the gel is found to correlate the degree of neovascularization in the gel.

In another preferred embodiment, the effect of the candidate modulator on MP53 is assessed via tumorigenicity assays. Tumor xenograft assays are known in the art (see, e.g., Ogawa K et al., 2000, *Oncogene* 19:6043-6052). Xenografts are typically implanted SC into female athymic mice, 6-7 week old, as single cell suspensions either from a pre-existing tumor or from *in vitro* culture. The tumors which express the MP53 endogenously are injected in the flank, 1×10^5 to 1×10^7 cells per mouse in a volume of 100 μ L using a 27gauge needle. Mice are then ear tagged and tumors are measured twice weekly. Candidate modulator treatment is initiated on the day the mean tumor weight reaches 100 mg. Candidate modulator is delivered IV, SC, IP, or PO by bolus administration. Depending upon the pharmacokinetics of each unique candidate modulator, dosing can be performed multiple times per day. The tumor weight is assessed by measuring perpendicular diameters with a caliper and calculated by multiplying the measurements of diameters in two dimensions. At the end of the experiment, the excised tumors maybe utilized for biomarker identification or further analyses. For immunohistochemistry staining, xenograft tumors are fixed in 4% paraformaldehyde, 0.1M phosphate, pH 7.2, for 6 hours at 4°C, immersed in 30% sucrose in PBS, and rapidly frozen in isopentane cooled with liquid nitrogen.

In another preferred embodiment, tumorigenicity is monitored using a hollow fiber assay, which is described in U.S. Pat No. US 5,698,413. Briefly, the method comprises implanting into a laboratory animal a biocompatible, semi-permeable encapsulation device containing target cells, treating the laboratory animal with a candidate modulating agent, and evaluating the target cells for reaction to the candidate modulator. Implanted cells are generally human cells from a pre-existing tumor or a tumor cell line. After an appropriate period of time, generally around six days, the implanted samples are harvested for evaluation of the candidate modulator. Tumorigenicity and modulator efficacy may be evaluated by assaying the quantity of viable cells present in the macrocapsule, which can be determined by tests known in the art, for example, MTT dye conversion assay, neutral

red dye uptake, trypan blue staining, viable cell counts, the number of colonies formed in soft agar, the capacity of the cells to recover and replicate in vitro, etc.

In another preferred embodiment, a tumorigenicity assay use a transgenic animal, usually a mouse, carrying a dominant oncogene or tumor suppressor gene knockout under the control of tissue specific regulatory sequences; these assays are generally referred to as transgenic tumor assays. In a preferred application, tumor development in the transgenic model is well characterized or is controlled. In an exemplary model, the "RIP1-Tag2" transgene, comprising the SV40 large T-antigen oncogene under control of the insulin gene regulatory regions is expressed in pancreatic beta cells and results in islet cell carcinomas (Hanahan D, 1985, Nature 315:115-122; Parangi S et al, 1996, Proc Natl Acad Sci USA 93: 2002-2007; Bergers G et al, 1999, Science 284:808-812). An "angiogenic switch," occurs at approximately five weeks, as normally quiescent capillaries in a subset of hyperproliferative islets become angiogenic. The RIP1-TAG2 mice die by age 14 weeks. Candidate modulators may be administered at a variety of stages, including just prior to the angiogenic switch (e.g., for a model of tumor prevention), during the growth of small tumors (e.g., for a model of intervention), or during the growth of large and/or invasive tumors (e.g., for a model of regression). Tumorigenicity and modulator efficacy can be evaluating life-span extension and/or tumor characteristics, including number of tumors, tumor size, tumor morphology, vessel density, apoptotic index, etc.

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Diagnostic and therapeutic uses

Specific MP53-modulating agents are useful in a variety of diagnostic and therapeutic applications where disease or disease prognosis is related to defects in the p53 pathway, such as angiogenic, apoptotic, or cell proliferation disorders. Accordingly, the invention also provides methods for modulating the p53 pathway in a cell, preferably a cell pre-determined to have defective or impaired p53 function (e.g. due to overexpression, underexpression, or misexpression of p53, or due to gene mutations), comprising the step of administering an agent to the cell that specifically modulates MP53 activity. Preferably, the modulating agent produces a detectable phenotypic change in the cell indicating that the p53 function is restored. The phrase "function is restored", and equivalents, as used herein, means that the desired phenotype is achieved, or is brought closer to normal compared to untreated cells. For example, with restored p53 function, cell proliferation and/or progression through cell cycle may normalize, or be brought closer to normal relative to untreated cells. The invention also provides methods for

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treating disorders or disease associated with impaired p53 function by administering a therapeutically effective amount of an MP53 -modulating agent that modulates the p53 pathway. The invention further provides methods for modulating MP53 function in a cell, preferably a cell pre-determined to have defective or impaired MP53 function, by
5 administering an MP53 -modulating agent. Additionally, the invention provides a method for treating disorders or disease associated with impaired MP53 function by administering a therapeutically effective amount of an MP53 -modulating agent.

The discovery that MP53 is implicated in p53 pathway provides for a variety of methods that can be employed for the diagnostic and prognostic evaluation of diseases and
10 disorders involving defects in the p53 pathway and for the identification of subjects having a predisposition to such diseases and disorders.

Various expression analysis methods can be used to diagnose whether MP53 expression occurs in a particular sample, including Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR, and microarray analysis. (e.g., Current
15 Protocols in Molecular Biology (1994) Ausubel FM *et al.*, eds., John Wiley & Sons, Inc., chapter 4; Freeman WM *et al.*, *Biotechniques* (1999) 26:112-125; Kallioniemi OP, *Ann Med* 2001, 33:142-147; Blohm and Guiseppe-Elie, *Curr Opin Biotechnol* 2001, 12:41-47). Tissues having a disease or disorder implicating defective p53 signaling that express an MP53, are identified as amenable to treatment with an MP53 modulating agent. In a
20 preferred application, the p53 defective tissue overexpresses an MP53 relative to normal tissue. For example, a Northern blot analysis of mRNA from tumor and normal cell lines, or from tumor and matching normal tissue samples from the same patient, using full or partial MP53 cDNA sequences as probes, can determine whether particular tumors express or overexpress MP53. Alternatively, the TaqMan® is used for quantitative RT-PCR
25 analysis of MP53 expression in cell lines, normal tissues and tumor samples (PE Applied Biosystems).

Various other diagnostic methods may be performed, for example, utilizing reagents such as the MP53 oligonucleotides, and antibodies directed against an MP53, as described above for: (1) the detection of the presence of MP53 gene mutations, or the
30 detection of either over- or under-expression of MP53 mRNA relative to the non-disorder state; (2) the detection of either an over- or an under-abundance of MP53 gene product relative to the non-disorder state; and (3) the detection of perturbations or abnormalities in the signal transduction pathway mediated by MP53.

Thus, in a specific embodiment, the invention is drawn to a method for diagnosing a disease or disorder in a patient that is associated with alterations in MP53 expression, the method comprising: a) obtaining a biological sample from the patient; b) contacting the sample with a probe for MP53 expression; c) comparing results from step (b) with a control; and d) determining whether step (c) indicates a likelihood of the disease or disorder. Preferably, the disease is cancer, most preferably a cancer as shown in TABLE 2. The probe may be either DNA or protein, including an antibody.

EXAMPLES

The following experimental section and examples are offered by way of illustration and not by way of limitation.

I. Drosophila p53 screen

The *Drosophila* p53 gene was overexpressed specifically in the wing using the vestigial margin quadrant enhancer. Increasing quantities of *Drosophila* p53 (titrated using different strength transgenic inserts in 1 or 2 copies) caused deterioration of normal wing morphology from mild to strong, with phenotypes including disruption of pattern and polarity of wing hairs, shortening and thickening of wing veins, progressive crumpling of the wing and appearance of dark "death" inclusions in wing blade. In a screen designed to identify enhancers and suppressors of *Drosophila* p53, homozygous females carrying two copies of p53 were crossed to 5663 males carrying random insertions of a piggyBac transposon (Fraser M *et al.*, Virology (1985) 145:356-361). Progeny containing insertions were compared to non-insertion-bearing sibling progeny for enhancement or suppression of the p53 phenotypes. Sequence information surrounding the piggyBac insertion site was used to identify the modifier genes. Modifiers of the wing phenotype were identified as members of the p53 pathway. Modifiers (enhancers and suppressors of the wing phenotype). Orthologs of the modifiers are referred to herein as MP53.

II. Analysis of Table 1

BLAST analysis (Altschul et al., *supra*) was employed to identify orthologs of *Drosophila* modifiers. The columns "MP53 symbol", "MP53 name" and "MP53 name aliases" provide a symbol and the known name abbreviations for the Targets, where available, from Genbank. "MP53 RefSeq_NA or GI_NA", and "MP53 GI_AA", provide the reference nucleotide and amino acid sequences for the MP53s as available from

National Center for Biology Information (NCBI), and Genbank, where available.

Nucleotide and amino acid SEQ ID Nos of the sequences used in the application are also provided.

Names and Protein sequences of *Drosophila* modifiers of p53 from screen

- 5 (Example I), are represented in the "Modifier genetic Name", "Modifier physical Name" and "Modifier GI_AA" column by GI#, respectively.

Table 1

MP53 Symbol	MP53 name	MP53 name aliases	MP53 identifier NA RefSeq or GI#	NA SEQ ID NO.	MP53 GI# AA	AA SEQ ID NO.	Modifier genetic name	Modifier physical name	Modifier GI# AA
ANXA13	annexin A13	ANX13	XM_052383	1	4757754	57	AnnIX_(Annexin IX)	CG5730	gi 17136266 ref NP_476604.1
ANXA4	annexin A4	ANX4	NM_001153	2	4502105	58	AnnIX_(Annexin IX)	CG5730	gi 17136266 ref NP_476604.1
AXOT	axotrophin	DKFZP586F1122; axotrophin	NM_022826	3	12383066	59	NA	CG14518	gi 7301726 gb AAF56839.1
FLJ20085	hypothetical protein FLJ20085	-	XM_053238.1	4	15308522	60	NA	CG7983	gi 7294806 gb AAF50140.1
NYX	nyctalopin, alias: congenital stationary night blindness 4; Congenital stationary night blindness-1 (CSNB, complete)	dJ169I5.2, CLR P, CSNB1, CSNB4	NM_022567	5	12314287	61	caps_(capricious)	CG11282	gi 3885974 gb AAC78144.1
FLJ21302	hypothetical protein FLJ21302	-	NM_022901	6	12597641	62	caps_(capricious)	CG11282	gi 3885974 gb AAC78144.1
GARP	glycoprotein A repetitions predominant	D11S833E	XM_006198	7	5031707	63	caps_(capricious)	CG11282	gi 3885974 gb AAC78144.1
GP1BA	glycoprotein Ib (platelet), alpha polypeptide	CD42b	NM_000173	8	4504071	64	caps_(capricious)	CG11282	gi 3885974 gb AAC78144.1
GP5	glycoprotein V (platelet)	CD42d	XM_002975	9	4758460	65	caps_(capricious)	CG11282	gi 3885974 gb AAC78144.1
HT017	HT017 protein	-	XM_054557	10	10190722	66	caps_(capricious)	CG11282	gi 3885974 gb AAC78144.1

KIAA0416	KIAA0416 protein		XM_003637	11	7662102	67	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
LY64	lymphocyte antigen 64 homolog, radioprotective 105kD (mouse)	RP105	XM_003933	12	13645378	68	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
LOC112684			XM_053144.1	13	15301270	69	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
ISLR			NM_005545.1	14	5031809	70	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
Unknown (protein for MGC:17113)			15489167	15	15489168	71	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
unnamed protein product CAC21785			12226531	16	12226532	72	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
KIAA1465			XM_027396.1	17	14752075	73	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
LOC115025			XM_028612.2	18	15294652	74	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
PAL			NM_015613.1	19	14149694	75	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
KIAA1246			XM_046690.2	20	15300859	76	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
MGC2656			NM_024509.1	21	13375646	77	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
unnamed protein product CAC49977			15132048	22	15132049	78	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
KIAA1910			XM_055514.1	23	16163269	79	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
KIAA0918			XM_054870.1	24	16188327	80	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
bG25602.2.1			5531259	25	6691962	81	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
KIAA0848			NM_014926.1	26	7662336	82	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1
CASK			NM_003688.1	27	4502567	83	caps_(capricious)	CG11282	gi 3885974 gb AAC7814.4.1

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LIN-7-C		LIN-7- C: LIN- 7 protein 3	NM_018362 .1	29	8922944	85	caps_(capr icious)	CG11282	gi 3885974 g b AAC7814 4.1
TRIM3	tripartite motif- containing 3	RNF22	XM_044513	30	5453569	86	brat_(brai n_tumor)	CG10719	gi 17136846 ref NP_4769 45.1
LBP-32	LBP protein 32	none	NM_014552	31	7657297	87	grh_grain yhead	CG2094	7302703
PTBP2	polypyrimidi ne tract binding protein 2	PTB, MIBP, nPTB, PTBLP, neural polypyri midine tract binding protein	XM_042972	32	14722543	88	heph_hep haustus	CG2094	7302108
ROD1	ROD1 regulator of differentiatio n 1 (S. pombe)		NM_005156	33	4826984	89	heph_hep haustus	CG2094	7302108
PTBP1	polypyrimidi ne tract binding protein 1	PTB; PTB2; PTB3; PTB4; pPTB; HNRPI; PTB-1; HNRNP I	NM_002819	34	4506243	90	heph_hep haustus	CG2094	7302108
P4HA1	procollagen- proline, 2- oxoglutarate 4- dioxygenase (proline 4- hydroxylase), alpha polypeptide I	P4HA	NM_000917	35	4505565	91	none	SD05564p	15292529
P4HA2	procollagen- proline, 2- oxoglutarate 4- dioxygenase (proline 4- hydroxylase), alpha polypeptide III	prolyl 4- hydroxy lase, alpha polypep tide, type 2; prolyl 4-	NM_004199	36	4758868	92	none	SD05564p	15292529

		hydroxy lase, alpha polypep tide, type II							
none	metastasis suppressor protein	none	6539605	37	6539606	93	none	CG9469	7302324
LOC92154	similar to Unknown (protein for IMAGE)	none	XM_043228	38	14779986	94	none	CG9469	7302324
LOC123676	similar to hypothetical protein, MNCb-1213 (H. sapiens)	none	XM_063793	39	17478005	95	none	CG5447	18488547
LOC51125	HSPC041 protein	none	NM_016099	40	7705821	96	none	CG5447	18488547
WFS1	Wolfram syndrome 1 (wolframin)	WFS, WFRS, DIDMO AD	NM_006005	41	5174749	97	none	mod_@tra nsmembra ne wolfram syndrome wolframin transcript _3 translation	Exelixis internal
PPP1R16A	protein phosphatase 1, regulatory (inhibitor) subunit 16A	MYPT3 , MGC14 333; likely ortholog of mouse myosin phospha tase targetin g subunit 3	NM_032902	42	14249672	98	none	CG6896	7293882
PPP1R16B	protein phosphatase 1, regulatory (inhibitor) subunit 16B	TIMAP, ANKR D4, KIAA0 823	XM_028840	43	14770818	99	none	CG6896	7293882
CXorf9	chromosome X open reading frame 9	SLY, 753P9; likely ortholog of mouse SH3 gene SLY	NM_018990	44	9506363	100	none	mod_@ki aa0790.tra nscript_11 translation	Exelixis internal

LOC134963	similar to KIAA0790 protein (H. sapiens)	none	XM_044015	45	14751637	101	none	mod_@ki aa0790.transcript_11 translation	Exelixis internal
SAMSN1	SAM domain, SH3 domain and nuclear localisation signals, 1	none	NM_022136	46	11545871	102	none	mod_@ki aa0790.transcript_11 translation	Exelixis internal
MGC9564	similar to RIKEN cDNA 1110002C08 gene		NM_080669	47	18087847	103	none	CG15553	7302010
FKSG16	none	none	16416763	48	16416764	104	none	CG15553	7302010
BAG3	BCL2-associated athanogene 3	BIS, BAG-3, CAIR-1, DKFZp434E0610; Bcl-2-binding protein; docking protein CAIR-1; BCL2-binding athanogene 3; BAG-family molecular chaperone regulator-3	NM_004281	49	14043024	105	none	CG10745	16076828
BAG4	BCL2-associated athanogene 4	SODD, BAG-4; silencer of death domains; BAG-family molecular chaperone regulator-4	NM_004874	50	6631075	106	none	CG10745	16076828
FLJ22944	hypothetical protein FLJ22944		NM_025145	51	13376733	107	none	mod_@dk fzp434a2017 flj11142.transcript_3	Exelixis internal

								translation	
FLJ11142	hypothetical protein FLJ11142		NM_018338	52	8922897	108	none	mod_@dk fzp434a20 17 flj11142.tr anscript_3 translation	Exelixis internal
BAZ1A	bromodomain adjacent to zinc finger domain, 1A	ACF1, WALP1, hACF1, WCRF180, DKFZP586E0518	NM_013448	53	7304919	109	Acfl_AT P-dependent chromatin assembly factor large subunit	CG1966	7302099
BAZ1B	bromodomain adjacent to zinc finger domain, 1B	WSTF, WBSCR9, WBSCR10; Williams-Beuren syndrome chromosome region	NM_023005	54	14670390	110	Acfl_AT P-dependent chromatin assembly factor large subunit	CG1966	7302099
FLJ21613	hypothetical protein FLJ21613 similar to rat corneal wound healing related protein	none	NM_021929	55	11345464	111	none	CG4065	7291750
KIAA0483	KIAA0483 protein	none	NM_015176	56	7022998	112	none	CG3428	7294925

III. High-Throughput In Vitro Fluorescence Polarization Assay

Fluorescently-labeled MP53 peptide/substrate are added to each well of a 96-well microtiter plate, along with a test agent in a test buffer (10 mM HEPES, 10 mM NaCl, 6 mM magnesium chloride, pH 7.6). Changes in fluorescence polarization, determined by using a Fluorolite FPM-2 Fluorescence Polarization Microtiter System (Dynatech Laboratories, Inc), relative to control values indicates the test compound is a candidate modifier of MP53 activity.

IV. High-Throughput In Vitro Binding Assay.

³³P-labeled MP53 peptide is added in an assay buffer (100 mM KCl, 20 mM HEPES pH 7.6, 1 mM MgCl₂, 1% glycerol, 0.5% NP-40, 50 mM beta-mercaptoethanol, 1 mg/ml BSA, cocktail of protease inhibitors) along with a test agent to the wells of a
5 Neutralite-avidin coated assay plate and incubated at 25°C for 1 hour. Biotinylated substrate is then added to each well and incubated for 1 hour. Reactions are stopped by washing with PBS, and counted in a scintillation counter. Test agents that cause a difference in activity relative to control without test agent are identified as candidate p53 modulating agents.

10

V. Immunoprecipitations and Immunoblotting

For coprecipitation of transfected proteins, 3×10^6 appropriate recombinant cells containing the MP53 proteins are plated on 10-cm dishes and transfected on the following day with expression constructs. The total amount of DNA is kept constant in each
15 transfection by adding empty vector. After 24 h, cells are collected, washed once with phosphate-buffered saline and lysed for 20 min on ice in 1 ml of lysis buffer containing 50 mM Hepes, pH 7.9, 250 mM NaCl, 20 mM -glycerophosphate, 1 mM sodium orthovanadate, 5 mM p-nitrophenyl-phosphate, 2 mM dithiothreitol, protease inhibitors (complete, Roche Molecular Biochemicals), and 1% Nonidet P-40. Cellular debris is
20 removed by centrifugation twice at $15,000 \times g$ for 15 min. The cell lysate is incubated with 25 μ l of M2 beads (Sigma) for 2 h at 4 °C with gentle rocking.

After extensive washing with lysis buffer, proteins bound to the beads are solubilized by boiling in SDS sample buffer, fractionated by SDS-polyacrylamide gel electrophoresis, transferred to polyvinylidene difluoride membrane and blotted with the
25 indicated antibodies. The reactive bands are visualized with horseradish peroxidase coupled to the appropriate secondary antibodies and the enhanced chemiluminescence (ECL) Western blotting detection system (Amersham Pharmacia Biotech).

VI. Kinase assay

30 A purified or partially purified MP53 is diluted in a suitable reaction buffer, e.g., 50 mM Hepes, pH 7.5, containing magnesium chloride or manganese chloride (1-20 mM) and a peptide or polypeptide substrate, such as myelin basic protein or casein (1-10 μ g/ml). The final concentration of the kinase is 1-20 nM. The enzyme reaction is conducted in microtiter plates to facilitate optimization of reaction conditions by

'increasing assay throughput. A 96-well microtiter plate is employed using a final volume 30-100 μ l. The reaction is initiated by the addition of ^{33}P -gamma-ATP (0.5 $\mu\text{Ci/ml}$) and incubated for 0.5 to 3 hours at room temperature. Negative controls are provided by the addition of EDTA, which chelates the divalent cation (Mg^{2+} or Mn^{2+}) required for enzymatic activity. Following the incubation, the enzyme reaction is quenched using EDTA. Samples of the reaction are transferred to a 96-well glass fiber filter plate (MultiScreen, Millipore). The filters are subsequently washed with phosphate-buffered saline, dilute phosphoric acid (0.5%) or other suitable medium to remove excess radiolabeled ATP. Scintillation cocktail is added to the filter plate and the incorporated radioactivity is quantitated by scintillation counting (Wallac/Perkin Elmer). Activity is defined by the amount of radioactivity detected following subtraction of the negative control reaction value (EDTA quench).

VII. Expression analysis

All cell lines used in the following experiments are NCI (National Cancer Institute) lines, and are available from ATCC (American Type Culture Collection, Manassas, VA 20110-2209). Normal and tumor tissues were obtained from Impath, UC Davis, Clontech, Stratagene, Ardaïs, Genome Collaborative, and Ambion.

TaqMan analysis was used to assess expression levels of the disclosed genes in various samples.

RNA was extracted from each tissue sample using Qiagen (Valencia, CA) RNeasy kits, following manufacturer's protocols, to a final concentration of 50ng/ μ l. Single stranded cDNA was then synthesized by reverse transcribing the RNA samples using random hexamers and 500ng of total RNA per reaction, following protocol 4304965 of Applied Biosystems (Foster City, CA).

Primers for expression analysis using TaqMan assay (Applied Biosystems, Foster City, CA) were prepared according to the TaqMan protocols, and the following criteria: a) primer pairs were designed to span introns to eliminate genomic contamination, and b) each primer pair produced only one product. Expression analysis was performed using a 7900HT instrument.

Taqman reactions were carried out following manufacturer's protocols, in 25 μ l total volume for 96-well plates and 10 μ l total volume for 384-well plates, using 300nM primer and 250 nM probe, and approximately 25ng of cDNA. The standard curve for result analysis was prepared using a universal pool of human cDNA samples, which is a

mixture of cDNAs from a wide variety of tissues so that the chance that a target will be present in appreciable amounts is good. The raw data were normalized using 18S rRNA (universally expressed in all tissues and cells).

For each expression analysis, tumor tissue samples were compared with matched
5 normal tissues from the same patient. A gene was considered overexpressed in a tumor when the level of expression of the gene was 2 fold or higher in the tumor compared with its matched normal sample. In cases where normal tissue was not available, a universal pool of cDNA samples was used instead. In these cases, a gene was considered
10 overexpressed in a tumor sample when the difference of expression levels between a tumor sample and the average of all normal samples from the same tissue type was greater than 2 times the standard deviation of all normal samples (i.e., $\text{Tumor} - \text{average}(\text{all normal samples}) > 2 \times \text{STDEV}(\text{all normal samples})$).

Results are shown in Table 2. Number of pairs of tumor samples and matched
normal tissue from the same patient are shown for each tumor type. Percentage of the
15 samples with at least two-fold overexpression for each tumor type is provided. ND indicates not done. A modulator identified by an assay described herein can be further validated for therapeutic effect by administration to a tumor in which the gene is overexpressed. A decrease in tumor growth confirms therapeutic utility of the modulator. Prior to treating a patient with the modulator, the likelihood that the patient will respond to
20 treatment can be diagnosed by obtaining a tumor sample from the patient, and assaying for expression of the gene targeted by the modulator. The expression data for the gene(s) can also be used as a diagnostic marker for disease progression. The assay can be performed by expression analysis as described above, by antibody directed to the gene target, or by any other available detection method.

25

Table 2

SEQ ID NO	Brea st	# of Pai rs	Colo n	# of Pai rs	Head and Neck	# of Pai rs	Kidn ey	# of Pai rs	Lung	# of Pai rs	Ovary	# of Pai rs	Pros tate	# of Pai rs	Skin	# of Pai rs	Uteri s	# of Pai rs
48	5%	21	6%	33	12%	8	12%	24	5%	21	9%	11	17%	12	0%	3	11%	19
52	5%	21	6%	33	12%	8	8%	24	0%	21	9%	11	17%	12	0%	3	21%	19
4	5%	21	6%	33	12%	8	8%	24	0%	21	9%	11	17%	12	0%	3	21%	19
6	33%	6	17%	30	ND	ND	ND	ND	8%	12	20%	5	ND	ND	ND	ND	ND	ND
55	33%	6	17%	30	ND	ND	ND	ND	8%	12	20%	5	ND	ND	ND	ND	ND	ND
51	33%	6	17%	30	ND	ND	ND	ND	8%	12	20%	5	ND	ND	ND	ND	ND	ND
7	0%	12	50%	30	ND	ND	ND	ND	0%	14	14%	7	ND	ND	ND	ND	ND	ND
8	33%	12	10%	29	ND	ND	ND	ND	21%	14	29%	7	ND	ND	ND	ND	ND	ND
9	8%	12	33%	30	ND	ND	ND	ND	7%	14	14%	7	ND	ND	ND	ND	ND	ND
10	100 %	1	0%	8	ND	ND	ND	ND	0%	2	ND	ND	ND	ND	ND	ND	ND	ND
11	0%	12	7%	28	ND	ND	ND	ND	7%	14	14%	7	ND	ND	ND	ND	ND	ND
56	0%	12	7%	28	ND	ND	ND	ND	7%	14	14%	7	ND	ND	ND	ND	ND	ND
31	5%	21	6%	33	25%	8	12%	24	5%	21	0%	11	8%	12	33%	3	5%	19
40	17%	18	22%	23	25%	8	20%	20	6%	18	10%	10	0%	8	33%	3	20%	15
38	17%	18	22%	23	25%	8	20%	20	6%	18	10%	10	0%	8	33%	3	20%	15
12	25%	12	17%	30	ND	ND	ND	ND	21%	14	0%	6	ND	ND	ND	ND	ND	ND
47	14%	21	18%	33	25%	8	29%	24	5%	21	10%	10	8%	12	67%	3	0%	19
5	8%	12	14%	14	ND	ND	ND	ND	18%	11	14%	7	ND	ND	ND	ND	ND	ND
42	10%	21	15%	33	25%	8	12%	24	14%	21	18%	11	8%	12	67%	3	5%	19
43	10%	21	15%	33	25%	8	12%	24	14%	21	18%	11	8%	12	67%	3	5%	19
34	10%	21	15%	33	25%	8	12%	24	14%	21	18%	11	8%	12	67%	3	5%	19
32	10%	21	15%	33	25%	8	12%	24	14%	21	18%	11	8%	12	67%	3	5%	19
33	10%	21	15%	33	25%	8	12%	24	14%	21	18%	11	8%	12	67%	3	5%	19
30	33%	21	67%	33	25%	8	83%	24	10%	21	36%	11	17%	12	33%	3	58%	19

WHAT IS CLAIMED IS:

1. A method of identifying a candidate p53 pathway modulating agent, said method comprising the steps of:
 - 5 (a) providing an assay system comprising a MP53 polypeptide or nucleic acid;
 - (b) contacting the assay system with a test agent under conditions whereby, but for the presence of the test agent, the system provides a reference activity; and
 - (c) detecting a test agent-biased activity of the assay system, wherein a difference between the test agent-biased activity and the reference activity identifies the test agent as
 - 10 a candidate p53 pathway modulating agent.
2. The method of Claim 1 wherein the assay system comprises cultured cells that express the MP53 polypeptide.
- 15 3. The method of Claim 2 wherein the cultured cells additionally have defective p53 function.
4. The method of Claim 1 wherein the assay system includes a screening assay comprising a MP53 polypeptide, and the candidate test agent is a small molecule
- 20 modulator.
5. The method of Claim 4 wherein the assay is a binding assay.
6. The method of Claim 1 wherein the assay system is selected from the group consisting of an apoptosis assay system, a cell proliferation assay system, an angiogenesis assay
- 25 system, and a hypoxic induction assay system.
7. The method of Claim 1 wherein the assay system includes a binding assay comprising a MP53 polypeptide and the candidate test agent is an antibody.
- 30 8. The method of Claim 1 wherein the assay system includes an expression assay comprising a MP53 nucleic acid and the candidate test agent is a nucleic acid modulator.
9. The method of Claim 8 wherein the nucleic acid modulator is an antisense oligomer.

10. The method of Claim 8 wherein the nucleic acid modulator is a PMO.
11. The method of Claim 1 additionally comprising:
(d) administering the candidate p53 pathway modulating agent identified in (c) to a
5 model system comprising cells defective in p53 function and, detecting a phenotypic
change in the model system that indicates that the p53 function is restored.
12. The method of Claim 11 wherein the model system is a mouse model with defective
p53 function.
- 10 13. A method for modulating a p53 pathway of a cell comprising contacting a cell
defective in p53 function with a candidate modulator that specifically binds to a MP53
polypeptide, whereby p53 function is restored.
- 15 14. The method of Claim 13 wherein the candidate modulator is administered to a
vertebrate animal predetermined to have a disease or disorder resulting from a defect in
p53 function.
- 15 15. The method of Claim 13 wherein the candidate modulator is selected from the group
20 consisting of an antibody and a small molecule.
16. The method of Claim 1, comprising the additional steps of:
(e) providing a secondary assay system comprising cultured cells or a non-human
animal expressing MP53 ,
25 (f) contacting the secondary assay system with the test agent of (b) or an agent
derived therefrom under conditions whereby, but for the presence of the test agent or agent
derived therefrom, the system provides a reference activity; and
(g) detecting an agent-biased activity of the second assay system,
wherein a difference between the agent-biased activity and the reference activity of
30 the second assay system confirms the test agent or agent derived therefrom as a candidate
p53 pathway modulating agent,
and wherein the second assay detects an agent-biased change in the p53 pathway.

17. The method of Claim 16 wherein the secondary assay system comprises cultured cells.
18. The method of Claim 16 wherein the secondary assay system comprises a non-human
5 animal.
19. The method of Claim 18 wherein the non-human animal mis-expresses a p53 pathway gene.
- 10 20. A method of modulating p53 pathway in a mammalian cell comprising contacting the cell with an agent that specifically binds a MP53 polypeptide or nucleic acid.
21. The method of Claim 20 wherein the agent is administered to a mammalian animal predetermined to have a pathology associated with the p53 pathway.
- 15 22. The method of Claim 20 wherein the agent is a small molecule modulator, a nucleic acid modulator, or an antibody.
23. A method for diagnosing a disease in a patient comprising:
- 20 (a) obtaining a biological sample from the patient;
(b) contacting the sample with a probe for MP53 expression;
(c) comparing results from step (b) with a control;
(d) determining whether step (c) indicates a likelihood of disease.
- 25 24. The method of claim 23 wherein said disease is cancer.
25. The method according to claim 24, wherein said cancer is a cancer as shown in Table 2 as having >25% expression level.

30

SEQUENCE LISTING

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<211> 4932

<212> DNA

<213> Homo sapiens

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<211> 4726

<212> DNA

<213> Homo sapiens

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4726

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<210> 48

<211> 1748

<212> DNA

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Asp Leu Tyr Asp Ala Gly Glu Gly Arg Trp Gly Thr Asp Glu Leu Ala
 180 185 190

Phe Asn Glu Val Leu Ala Lys Arg Ser Tyr Lys Gln Leu Arg Ala Thr
 195 200 205

Phe Gln Ala Tyr Gln Ile Leu Ile Gly Lys Asp Ile Glu Glu Ala Ile
 210 215 220

Glu Glu Glu Thr Ser Gly Asp Leu Gln Lys Ala Tyr Leu Thr Leu Val
 225 230 235 240

Arg Cys Ala Gln Asp Cys Glu Asp Tyr Phe Ala Glu Arg Leu Tyr Lys
 245 250 255

Ser Met Lys Gly Ala Gly Thr Asp Glu Glu Thr Leu Ile Arg Ile Val
 260 265 270

Val Thr Arg Ala Glu Val Asp Leu Gln Gly Ile Lys Ala Lys Phe Gln
 275 280 285

Glu Lys Tyr Gln Lys Ser Leu Ser Asp Met Val Arg Ser Asp Thr Ser
 290 295 300

Gly Asp Phe Arg Lys Leu Leu Val Ala Leu Leu His
 305 310 315

<210> 58
 <211> 321
 <212> PRT
 <213> Homo sapiens

<400> 58

Met Ala Met Ala Thr Lys Gly Gly Thr Val Lys Ala Ala Ser Gly Phe
 1 5 10 15

Asn Ala Met Glu Asp Ala Gln Thr Leu Arg Lys Ala Met Lys Gly Leu
 20 25 30

Gly Thr Asp Glu Asp Ala Ile Ile Ser Val Leu Ala Tyr Arg Asn Thr
 35 40 45

Ala Gln Arg Gln Glu Ile Arg Thr Ala Tyr Lys Ser Thr Ile Gly Arg
 50 55 60

Asp Leu Ile Asp Asp Leu Lys Ser Glu Leu Ser Gly Asn Phe Glu Gln
 65 70 75 80

Val Ile Val Gly Met Met Thr Pro Thr Val Leu Tyr Asp Val Gln Glu
 85 90 95

Leu Arg Arg Ala Met Lys Gly Ala Gly Thr Asp Glu Gly Cys Leu Ile
 100 105 110
 Glu Ile Leu Ala Ser Arg Thr Pro Glu Glu Ile Arg Arg Ile Ser Gln
 115 120 125
 Thr Tyr Gln Gln Gln Tyr Gly Arg Ser Leu Glu Asp Asp Ile Arg Ser
 130 135 140
 Asp Thr Ser Phe Met Phe Gln Arg Val Leu Val Ser Leu Ser Ala Gly
 145 150 155 160
 Gly Arg Asp Glu Gly Asn Tyr Leu Asp Asp Ala Leu Val Arg Gln Asp
 165 170 175
 Ala Gln Asp Leu Tyr Glu Ala Gly Glu Lys Lys Trp Gly Thr Asp Glu
 180 185 190
 Val Lys Phe Leu Thr Val Leu Cys Ser Arg Asn Arg Asn His Leu Leu
 195 200 205
 His Val Phe Asp Glu Tyr Lys Arg Ile Ser Gln Lys Asp Ile Glu Gln
 210 215 220
 Ser Ile Lys Ser Glu Thr Ser Gly Ser Phe Glu Asp Ala Leu Leu Ala
 225 230 235 240
 Ile Val Lys Cys Met Arg Asn Lys Ser Ala Tyr Phe Ala Glu Lys Leu
 245 250 255
 Tyr Lys Ser Met Lys Gly Leu Gly Thr Asp Asp Asn Thr Leu Ile Arg
 260 265 270
 Val Met Val Ser Arg Ala Glu Ile Asp Met Leu Asp Ile Arg Ala His
 275 280 285
 Phe Lys Arg Leu Tyr Gly Lys Ser Leu Tyr Ser Phe Ile Lys Gly Asp
 290 295 300
 Thr Ser Gly Asp Tyr Arg Lys Val Leu Leu Val Leu Cys Gly Gly Asp
 305 310 315 320
 Asp

<211> 704

<212> PRT

<213> Homo sapiens

<400> 59

Met Glu Ser Lys Pro Ser Arg Ile Pro Arg Arg Ile Ser Val Gln Pro
 1 5 10 15

Ser Ser Ser Leu Ser Ala Arg Met Met Ser Gly Ser Arg Gly Ser Ser
 20 25 30

Leu Asn Asp Thr Tyr His Ser Arg Asp Ser Ser Phe Arg Leu Asp Ser
 35 40 45

Glu Tyr Gln Ser Thr Ser Ala Ser Ala Ser Ala Ser Pro Phe Gln Ser
 50 55 60

Ala Trp Tyr Ser Glu Ser Glu Ile Thr Gln Gly Ala Arg Ser Arg Ser
 65 70 75 80

Gln Asn Gln Gln Arg Asp His Asp Ser Lys Arg Pro Lys Leu Ser Cys
 85 90 95

Thr Asn Cys Thr Thr Ser Ala Gly Arg Asn Val Gly Asn Gly Leu Asn
 100 105 110

Thr Leu Ser Asp Ser Ser Trp Arg His Ser Gln Val Pro Arg Ser Ser
 115 120 125

Ser Met Val Leu Gly Ser Phe Gly Thr Asp Leu Met Arg Glu Arg Arg
 130 135 140

Asp Leu Glu Arg Arg Thr Asp Ser Ser Ile Ser Asn Leu Met Asp Tyr
 145 150 155 160

Ser His Arg Ser Gly Asp Phe Thr Thr Ser Ser Tyr Val Gln Asp Arg
 165 170 175

Val Pro Ser Tyr Ser Gln Gly Ala Arg Pro Lys Glu Asn Ser Met Ser
 180 185 190

Thr Leu Gln Leu Asn Thr Ser Ser Thr Asn His Gln Leu Pro Ser Glu
 195 200 205

His Gln Thr Ile Leu Ser Ser Arg Asp Ser Arg Asn Ser Leu Arg Ser
 210 215 220

Asn Phe Ser Ser Arg Glu Ser Glu Ser Ser Arg Ser Asn Thr Gln Pro
 225 230 235 240
 Gly Phe Ser Tyr Ser Ser Ser Arg Asp Glu Ala Pro Ile Ile Ser Asn
 245 250 255
 Ser Glu Arg Val Val Ser Ser Gln Arg Pro Phe Gln Glu Ser Ser Asp
 260 265 270
 Asn Glu Gly Arg Arg Thr Thr Arg Arg Leu Leu Ser Arg Ile Ala Ser
 275 280 285
 Ser Met Ser Ser Thr Phe Phe Ser Arg Arg Ser Ser Gln Asp Ser Leu
 290 295 300
 Asn Thr Arg Ser Leu Asn Ser Glu Asn Ser Tyr Val Ser Pro Arg Ile
 305 310 315 320
 Leu Thr Ala Ser Gln Ser Arg Ser Asn Val Pro Ser Ala Ser Glu Val
 325 330 335
 Pro Asp Asn Arg Ala Ser Glu Ala Ser Gln Gly Phe Arg Phe Leu Arg
 340 345 350
 Arg Arg Trp Gly Leu Ser Ser Leu Ser His Asn His Ser Ser Glu Ser
 355 360 365
 Asp Ser Glu Asn Phe Asn Gln Glu Ser Glu Gly Arg Asn Thr Gly Pro
 370 375 380
 Trp Leu Ser Ser Ser Leu Arg Asn Arg Cys Thr Pro Leu Phe Ser Arg
 385 390 395 400
 Arg Arg Arg Glu Gly Arg Asp Glu Ser Ser Arg Ile Pro Thr Ser Asp
 405 410 415
 Thr Ser Ser Arg Ser His Ile Phe Arg Arg Glu Ser Asn Glu Val Val
 420 425 430
 His Leu Glu Ala Gln Asn Asp Pro Leu Gly Ala Ala Ala Asn Arg Pro
 435 440 445
 Gln Ala Ser Ala Ala Ser Ser Ser Ala Thr Thr Gly Gly Ser Thr Ser
 450 455 460
 Asp Ser Ala Gln Gly Gly Arg Asn Thr Gly Ile Ser Gly Ile Leu Pro
 465 470 475 480

Gly Ser Leu Phe Arg Phe Ala Val Pro Pro Ala Leu Gly Ser Asn Leu
 485 490 495
 Thr Asp Asn Val Met Ile Thr Val Asp Ile Ile Pro Ser Gly Trp Asn
 500 505 510
 Ser Ala Asp Gly Lys Ser Asp Lys Thr Lys Ser Ala Pro Ser Arg Asp
 515 520 525
 Pro Glu Arg Leu Gln Lys Ile Lys Glu Ser Leu Leu Leu Glu Asp Ser
 530 535 540
 Glu Glu Glu Glu Gly Asp Leu Cys Arg Ile Cys Gln Met Ala Ala Ala
 545 550 555 560
 Ser Ser Ser Asn Leu Leu Ile Glu Pro Cys Lys Cys Thr Gly Ser Leu
 565 570 575
 Gln Tyr Val His Gln Asp Cys Met Lys Lys Trp Leu Gln Ala Lys Ile
 580 585 590
 Asn Ser Gly Ser Ser Leu Glu Ala Val Thr Thr Cys Glu Leu Cys Lys
 595 600 605
 Glu Lys Leu Glu Leu Asn Leu Glu Asp Phe Asp Ile His Glu Leu His
 610 615 620
 Arg Ala His Ala Asn Glu Gln Ala Glu Tyr Glu Phe Ile Ser Ser Gly
 625 630 635 640
 Leu Tyr Leu Val Val Leu Leu His Leu Cys Glu Gln Ser Phe Ser Asp
 645 650 655
 Met Met Gly Asn Thr Asn Glu Pro Ser Thr Arg Val Arg Phe Ile Asn
 660 665 670
 Leu Ala Arg Thr Leu Gln Ala His Met Glu Asp Leu Glu Thr Ser Glu
 675 680 685
 Asp Asp Ser Glu Glu Asp Gly Asp His Asn Arg Thr Phe Asp Ile Ala
 690 695 700

<210> 60
 <211> 490
 <212> PRT
 <213> Homo sapiens

<400> 60

Met Ile Lys Gln Leu Lys Glu Glu Leu Arg Leu Glu Glu Ala Lys Leu
 1 5 10 15

Val Leu Leu Lys Lys Leu Arg Gln Ser Gln Ile Gln Lys Glu Ala Thr
 20 25 30

Ala Gln Lys Pro Thr Gly Ser Val Gly Ser Thr Val Thr Thr Pro Pro
 35 40 45

Pro Leu Val Arg Gly Thr Gln Asn Ile Pro Ala Gly Lys Pro Ser Leu
 50 55 60

Gln Thr Ser Ser Ala Arg Met Pro Gly Ser Val Ile Pro Pro Pro Leu
 65 70 75 80

Val Arg Gly Gly Gln Gln Ala Ser Ser Lys Leu Gly Pro Gln Ala Ser
 85 90 95

Ser Gln Val Val Met Pro Pro Leu Val Arg Gly Ala Gln Gln Ile His
 100 105 110

Ser Ile Arg Gln His Ser Ser Thr Gly Pro Pro Pro Leu Leu Leu Ala
 115 120 125

Pro Arg Ala Ser Val Pro Ser Val Gln Ile Gln Gly Gln Arg Ile Ile
 130 135 140

Gln Gln Gly Leu Ile Arg Val Ala Asn Val Pro Asn Thr Ser Leu Leu
 145 150 155 160

Val Asn Ile Pro Gln Pro Thr Pro Ala Ser Leu Lys Gly Thr Thr Ala
 165 170 175

Thr Ser Ala Gln Ala Asn Ser Thr Pro Thr Ser Val Ala Ser Val Val
 180 185 190

Thr Ser Ala Glu Ser Pro Ala Ser Arg Gln Ala Ala Ala Lys Leu Ala
 195 200 205

Leu Arg Lys Gln Leu Glu Lys Thr Leu Leu Glu Ile Pro Pro Pro Lys
 210 215 220

Pro Pro Ala Pro Glu Met Asn Phe Leu Pro Ser Ala Ala Asn Asn Glu
 225 230 235 240

Phe Ile Tyr Leu Val Gly Leu Glu Glu Val Val Gln Asn Leu Leu Glu
245 250 255

Thr Gln Gly Arg Met Ser Ala Ala Thr Val Leu Ser Arg Glu Pro Tyr
260 265 270

Met Cys Ala Gln Cys Lys Thr Asp Phe Thr Cys Arg Trp Arg Glu Glu
275 280 285

Lys Ser Gly Ala Ile Met Cys Glu Asn Cys Met Thr Thr Asn Gln Lys
290 295 300

Lys Ala Leu Lys Val Glu His Thr Ser Arg Leu Lys Ala Ala Phe Val
305 310 315 320

Lys Ala Leu Gln Gln Glu Gln Glu Ile Glu Gln Arg Leu Leu Gln Gln
325 330 335

Gly Thr Ala Pro Ala Gln Ala Lys Ala Glu Pro Thr Ala Ala Pro His
340 345 350

Pro Val Leu Lys Gln Val Ile Lys Pro Arg Arg Lys Leu Ala Phe Arg
355 360 365

Ser Gly Glu Ala Arg Asp Trp Ser Asn Gly Ala Val Leu Gln Ala Ser
370 375 380

Ser Gln Leu Ser Arg Gly Ser Ala Thr Thr Pro Arg Gly Val Leu His
385 390 395 400

Thr Phe Ser Pro Ser Pro Lys Leu Gln Asn Ser Ala Ser Ala Thr Ala
405 410 415

Leu Val Ser Arg Thr Gly Arg His Ser Glu Arg Thr Val Ser Ala Gly
420 425 430

Lys Gly Ser Ala Thr Ser Asn Trp Lys Lys Thr Pro Leu Ser Thr Gly
435 440 445

Gly Thr Leu Ala Phe Val Ser Pro Ser Leu Ala Val His Lys Ser Ser
450 455 460

Ser Ala Val Asp Arg Gln Arg Glu Tyr Leu Leu Asp Met Ile Pro Pro
465 470 475 480

Arg Ser Ile Pro Gln Ser Ala Thr Trp Lys

485

490

<210> 61
 <211> 495
 <212> PRT
 <213> Homo sapiens

<400> 61

Met Ser Ser Glu Ile Pro Gln Gly Leu Gln Thr Thr Asn Pro Gln Gly
 1 5 10 15

His Ile Leu Val Phe Pro Asp Gln Thr Glu Ala Val Val Leu Gly Leu
 20 25 30

Pro Ser Ala Trp Ala Val Gly Ala Cys Ala Arg Ala Cys Pro Ala Ala
 35 40 45

Cys Ala Cys Ser Thr Val Glu Arg Gly Cys Ser Val Arg Cys Asp Arg
 50 55 60

Ala Gly Leu Leu Arg Val Pro Ala Glu Leu Pro Cys Glu Ala Val Ser
 65 70 75 80

Ile Asp Leu Asp Arg Asn Gly Leu Arg Phe Leu Gly Glu Arg Ala Phe
 85 90 95

Gly Thr Leu Pro Ser Leu Arg Arg Leu Ser Leu Arg His Asn Asn Leu
 100 105 110

Ser Phe Ile Thr Pro Gly Ala Phe Lys Gly Leu Pro Arg Leu Ala Glu
 115 120 125

Leu Arg Leu Ala His Asn Gly Asp Leu Arg Tyr Leu His Ala Arg Thr
 130 135 140

Phe Ala Ala Leu Ser Arg Leu Arg Arg Leu Asp Leu Ala Ala Cys Arg
 145 150 155 160

Leu Phe Ser Val Pro Glu Arg Leu Leu Ala Glu Leu Pro Ala Leu Arg
 165 170 175

Glu Leu Ala Ala Phe Asp Asn Leu Phe Arg Arg Val Pro Gly Ala Leu
 180 185 190

Arg Gly Leu Ala Asn Leu Thr His Ala His Leu Glu Arg Gly Arg Ile
 195 200 205

Glu Ala Val Ala Ser Ser Ser Leu Gln Gly Leu Arg Arg Leu Arg Ser
 210 215 220

Leu Ser Leu Gln Ala Asn Arg Val Arg Ala Val His Ala Gly Ala Phe
 225 230 235 240

Gly Asp Cys Gly Val Leu Glu His Leu Leu Leu Asn Asp Asn Leu Leu
 245 250 255

Ala Glu Leu Pro Ala Asp Ala Phe Arg Gly Leu Arg Arg Leu Arg Thr
 260 265 270

Leu Asn Leu Gly Gly Asn Ala Leu Asp Arg Val Ala Arg Ala Trp Phe
 275 280 285

Ala Asp Leu Ala Glu Leu Glu Leu Leu Tyr Leu Asp Arg Asn Ser Ile
 290 295 300

Ala Phe Val Glu Glu Gly Ala Phe Gln Asn Leu Ser Gly Leu Leu Ala
 305 310 315 320

Leu His Leu Asn Gly Asn Arg Leu Thr Val Leu Ala Trp Val Ala Phe
 325 330 335

Gln Pro Gly Phe Phe Leu Gly Arg Leu Phe Leu Phe Arg Asn Pro Trp
 340 345 350

Cys Cys Asp Cys Arg Leu Glu Trp Leu Arg Asp Trp Met Glu Gly Ser
 355 360 365

Gly Arg Val Thr Asp Val Pro Cys Ala Ser Pro Gly Ser Val Ala Gly
 370 375 380

Leu Asp Leu Ser Gln Val Thr Phe Gly Arg Ser Ser Asp Gly Leu Cys
 385 390 395 400

Val Asp Pro Glu Glu Leu Asn Leu Thr Thr Ser Ser Pro Gly Pro Ser
 405 410 415

Pro Glu Pro Ala Ala Thr Thr Val Ser Arg Phe Ser Ser Leu Leu Ser
 420 425 430

Lys Leu Leu Ala Pro Arg Val Pro Val Glu Glu Ala Ala Asn Thr Thr
 435 440 445

Gly Gly Leu Ala Asn Ala Ser Leu Ser Asp Ser Leu Ser Ser Arg Gly
 450 455 460

Val Gly Gly Ala Gly Arg Gln Pro Trp Phe Leu Leu Ala Ser Cys Leu
 465 470 475 480

Leu Pro Ser Val Ala Gln His Val Val Phe Gly Leu Gln Met Asp
 485 490 495

<210> 62
 <211> 370
 <212> PRT
 <213> Homo sapiens

<400> 62

Met Lys Val Thr Gly Ile Thr Ile Leu Phe Trp Pro Leu Ser Met Ile
 1 5 10 15

Leu Leu Ser Asp Lys Ile Gln Ser Ser Lys Arg Glu Val Gln Cys Asn
 20 25 30

Phe Thr Glu Lys Asn Tyr Thr Leu Ile Pro Ala Asp Ile Lys Lys Asp
 35 40 45

Val Thr Ile Leu Asp Leu Ser Tyr Asn Gln Ile Thr Leu Asn Gly Thr
 50 55 60

Asp Thr Arg Val Leu Gln Thr Tyr Phe Leu Leu Thr Glu Leu Tyr Leu
 65 70 75 80

Ile Glu Asn Lys Val Thr Ile Leu His Asn Asn Gly Phe Gly Asn Leu
 85 90 95

Ser Ser Leu Glu Ile Leu Asn Ile Cys Arg Asn Ser Ile Tyr Val Ile
 100 105 110

Gln Gln Gly Ala Phe Leu Gly Leu Asn Lys Leu Lys Gln Leu Tyr Leu
 115 120 125

Cys Gln Asn Lys Ile Glu Gln Leu Asn Ala Asp Val Phe Val Pro Leu
 130 135 140

Arg Ser Leu Lys Leu Leu Asn Leu Gln Gly Asn Leu Ile Ser Tyr Leu
 145 150 155 160

Asp Val Pro Pro Leu Phe His Leu Glu Leu Ile Thr Leu Tyr Gly Asn
 165 170 175

Leu Trp Asn Cys Ser Cys Ser Leu Phe Asn Leu Gln Asn Trp Leu Asn

180 185 190
 Thr Ser Asn Val Thr Leu Glu Asn Glu Asn Ile Thr Met Cys Ser Tyr
 195 200 205
 Pro Asn Ser Leu Gln Ser Tyr Asn Ile Lys Thr Val Pro His Lys Ala
 210 215 220
 Glu Cys His Ser Lys Phe Pro Ser Ser Val Thr Glu Asp Leu Tyr Ile
 225 230 235 240
 His Phe Gln Pro Ile Ser Asn Ser Ile Phe Asn Ser Ser Ser Asn Asn
 245 250 255
 Leu Thr Arg Asn Ser Glu His Glu Pro Leu Gly Lys Ser Trp Ala Phe
 260 265 270
 Leu Val Gly Val Val Val Thr Val Leu Thr Thr Ser Leu Leu Ile Phe
 275 280 285
 Ile Ala Ile Lys Cys Pro Ile Trp Tyr Asn Ile Leu Leu Ser Tyr Asn
 290 295 300
 His His Arg Leu Glu Glu His Glu Ala Glu Thr Tyr Glu Asp Gly Phe
 305 310 315 320
 Thr Gly Asn Pro Ser Ser Leu Ser Gln Ile Pro Glu Thr Asn Ser Glu
 325 330 335
 Glu Thr Thr Val Ile Phe Glu Gln Leu His Ser Phe Val Val Asp Asp
 340 345 350
 Asp Gly Phe Ile Glu Asp Lys Tyr Ile Asp Ile His Glu Leu Cys Glu
 355 360 365
 Glu Asn
 370
 <210> 63
 <211> 662
 <212> PRT
 <213> Homo sapiens
 <400> 63
 Met Arg Pro Gln Ile Leu Leu Leu Leu Ala Leu Leu Thr Leu Gly Leu
 1 5 10 15

Ala Ala Gln His Gln Asp Lys Val Pro Cys Lys Met Val Asp Lys Lys
 20 25 30

Val Ser Cys Gln Val Leu Gly Leu Leu Gln Val Pro Ser Val Leu Pro
 35 40 45

Pro Asp Thr Glu Thr Leu Asp Leu Ser Gly Asn Gln Leu Arg Ser Ile
 50 55 60

Leu Ala Ser Pro Leu Gly Phe Tyr Thr Ala Leu Arg His Leu Asp Leu
 65 70 75 80

Ser Thr Asn Glu Ile Ser Phe Leu Gln Pro Gly Ala Phe Gln Ala Leu
 85 90 95

Thr His Leu Glu His Leu Ser Leu Ala His Asn Arg Leu Ala Met Ala
 100 105 110

Thr Ala Leu Ser Ala Gly Gly Leu Gly Pro Leu Pro Arg Val Thr Ser
 115 120 125

Leu Asp Leu Ser Gly Asn Ser Leu Tyr Ser Gly Leu Leu Glu Arg Leu
 130 135 140

Leu Gly Glu Ala Pro Ser Leu His Thr Leu Ser Leu Ala Glu Asn Ser
 145 150 155 160

Leu Thr Arg Leu Thr Arg His Thr Phe Arg Asp Met Pro Ala Leu Glu
 165 170 175

Gln Leu Asp Leu His Ser Asn Val Leu Met Asp Ile Glu Asp Gly Ala
 180 185 190

Phe Glu Gly Leu Pro Arg Leu Thr His Leu Asn Leu Ser Arg Asn Ser
 195 200 205

Leu Thr Cys Ile Ser Asp Phe Ser Leu Gln Gln Leu Arg Val Leu Asp
 210 215 220

Leu Ser Cys Asn Ser Ile Glu Ala Phe Gln Thr Ala Ser Gln Pro Gln
 225 230 235 240

Ala Glu Phe Gln Leu Thr Trp Leu Asp Leu Arg Glu Asn Lys Leu Leu
 245 250 255

His Phe Pro Asp Leu Ala Ala Leu Pro Arg Leu Ile Tyr Leu Asn Leu
 260 265 270

Ser Asn Asn Leu Ile Arg Leu Pro Thr Gly Pro Pro Gln Asp Ser Lys
 275 280 285

Gly Ile His Ala Pro Ser Glu Gly Trp Ser Ala Leu Pro Leu Ser Ala
 290 295 300

Pro Ser Gly Asn Ala Ser Gly Arg Pro Leu Ser Gln Leu Leu Asn Leu
 305 310 315 320

Asp Leu Ser Tyr Asn Glu Ile Glu Leu Ile Pro Asp Ser Phe Leu Glu
 325 330 335

His Leu Thr Ser Leu Cys Phe Leu Asn Leu Ser Arg Asn Cys Leu Arg
 340 345 350

Thr Phe Glu Ala Arg Arg Leu Gly Ser Leu Pro Cys Leu Met Leu Leu
 355 360 365

Asp Leu Ser His Asn Ala Leu Glu Thr Leu Glu Leu Gly Ala Arg Ala
 370 375 380

Leu Gly Ser Leu Arg Thr Leu Leu Leu Gln Gly Asn Ala Leu Arg Asp
 385 390 395 400

Leu Pro Pro Tyr Thr Phe Ala Asn Leu Ala Ser Leu Gln Arg Leu Asn
 405 410 415

Leu Gln Gly Asn Arg Val Ser Pro Cys Gly Gly Pro Asp Glu Pro Gly
 420 425 430

Pro Ser Gly Cys Val Ala Phe Ser Gly Ile Thr Ser Leu Arg Ser Leu
 435 440 445

Ser Leu Val Asp Asn Glu Ile Glu Leu Leu Arg Ala Gly Ala Phe Leu
 450 455 460

His Thr Pro Leu Thr Glu Leu Asp Leu Ser Ser Asn Pro Gly Leu Glu
 465 470 475 480

Val Ala Thr Gly Ala Leu Gly Gly Leu Glu Ala Ser Leu Glu Val Leu
 485 490 495

Ala Leu Gln Gly Asn Gly Leu Met Val Leu Gln Val Asp Leu Pro Cys
 500 505 510

Phe Ile Cys Leu Lys Arg Leu Asn Leu Ala Glu Asn Arg Leu Ser His
 515 520 525

Leu Pro Ala Trp Thr Gln Ala Val Ser Leu Glu Val Leu Asp Leu Arg
 530 535 540

Asn Asn Ser Phe Ser Leu Leu Pro Gly Ser Ala Met Gly Gly Leu Glu
 545 550 555 560

Thr Ser Leu Arg Arg Leu Tyr Leu Gln Gly Asn Pro Leu Ser Cys Cys
 565 570 575

Gly Asn Gly Trp Leu Ala Ala Gln Leu His Gln Gly Arg Val Asp Val
 580 585 590

Asp Ala Thr Gln Asp Leu Ile Cys Arg Phe Ser Ser Gln Glu Glu Val
 595 600 605

Ser Leu Ser His Val Arg Pro Glu Asp Cys Glu Lys Gly Gly Leu Lys
 610 615 620

Asn Ile Asn Leu Ile Ile Ile Leu Thr Phe Ile Leu Val Ser Ala Ile
 625 630 635 640

Leu Leu Thr Thr Leu Ala Ala Cys Cys Cys Val Arg Arg Gln Lys Phe
 645 650 655

Asn Gln Gln Tyr Lys Ala
 660

<210> 64
 <211> 626
 <212> PRT
 <213> Homo sapiens

<400> 64

Met Pro Leu Leu Leu Leu Leu Leu Leu Leu Pro Ser Pro Leu His Pro
 1 5 10 15

His Pro Ile Cys Glu Val Ser Lys Val Ala Ser His Leu Glu Val Asn
 20 25 30

Cys Asp Lys Arg Asn Leu Thr Ala Leu Pro Pro Asp Leu Pro Lys Asp
 35 40 45

Thr Thr Ile Leu His Leu Ser Glu Asn Leu Leu Tyr Thr Phe Ser Leu
 50 55 60

Ala Thr Leu Met Pro Tyr Thr Arg Leu Thr Gln Leu Asn Leu Asp Arg
 65 70 75 80

Cys Glu Leu Thr Lys Leu Gln Val Asp Gly Thr Leu Pro Val Leu Gly
 85 90 95

Thr Leu Asp Leu Ser His Asn Gln Leu Gln Ser Leu Pro Leu Leu Gly
 100 105 110

Gln Thr Leu Pro Ala Leu Thr Val Leu Asp Val Ser Phe Asn Arg Leu
 115 120 125

Thr Ser Leu Pro Leu Gly Ala Leu Arg Gly Leu Gly Glu Leu Gln Glu
 130 135 140

Leu Tyr Leu Lys Gly Asn Glu Leu Lys Thr Leu Pro Pro Gly Leu Leu
 145 150 155 160

Thr Pro Thr Pro Lys Leu Glu Lys Leu Ser Leu Ala Asn Asn Asn Leu
 165 170 175

Thr Glu Leu Pro Ala Gly Leu Leu Asn Gly Leu Glu Asn Leu Asp Thr
 180 185 190

Leu Leu Leu Gln Glu Asn Ser Leu Tyr Thr Ile Pro Lys Gly Phe Phe
 195 200 205

Gly Ser His Leu Leu Pro Phe Ala Phe Leu His Gly Asn Pro Trp Leu
 210 215 220

Cys Asn Cys Glu Ile Leu Tyr Phe Arg Arg Trp Leu Gln Asp Asn Ala
 225 230 235 240

Glu Asn Val Tyr Val Trp Lys Gln Gly Val Asp Val Lys Ala Met Thr
 245 250 255

Ser Asn Val Ala Ser Val Gln Cys Asp Asn Ser Asp Lys Phe Pro Val
 260 265 270

Tyr Lys Tyr Pro Gly Lys Gly Cys Pro Thr Leu Gly Asp Glu Gly Asp
 275 280 285

Thr Asp Leu Tyr Asp Tyr Tyr Pro Glu Glu Asp Thr Glu Gly Asp Lys
 290 295 300

Val Arg Ala Thr Arg Thr Val Val Lys Phe Pro Thr Lys Ala His Thr

305 310 315 320
 Thr Pro Trp Gly Leu Phe Tyr Ser Trp Ser Thr Ala Ser Leu Asp Ser
 325 330 335
 Gln Met Pro Ser Ser Leu His Pro Thr Gln Glu Ser Thr Lys Glu Gln
 340 345 350
 Thr Thr Phe Pro Pro Arg Trp Thr Pro Asn Phe Thr Leu His Met Glu
 355 360 365
 Ser Ile Thr Phe Ser Lys Thr Pro Lys Ser Thr Thr Glu Pro Thr Pro
 370 375 380
 Ser Pro Thr Thr Ser Glu Pro Val Pro Glu Pro Ala Pro Asn Met Thr
 385 390 395 400
 Thr Leu Glu Pro Thr Pro Ser Pro Thr Thr Pro Glu Pro Thr Ser Glu
 405 410 415
 Pro Ala Pro Ser Pro Thr Thr Pro Glu Pro Thr Pro Ile Pro Thr Ile
 420 425 430
 Ala Thr Ser Pro Thr Ile Leu Val Ser Ala Thr Ser Leu Ile Thr Pro
 435 440 445
 Lys Ser Thr Phe Leu Thr Thr Thr Lys Pro Val Ser Leu Leu Glu Ser
 450 455 460
 Thr Lys Lys Thr Ile Pro Glu Leu Asp Gln Pro Pro Lys Leu Arg Gly
 465 470 475 480
 Val Leu Gln Gly His Leu Glu Ser Ser Arg Asn Asp Pro Phe Leu His
 485 490 495
 Pro Asp Phe Cys Cys Leu Leu Pro Leu Gly Phe Tyr Val Leu Gly Leu
 500 505 510
 Phe Trp Leu Leu Phe Ala Ser Val Val Leu Ile Leu Leu Leu Ser Trp
 515 520 525
 Val Gly His Val Lys Pro Gln Ala Leu Asp Ser Gly Gln Gly Ala Ala
 530 535 540
 Leu Thr Thr Ala Thr Gln Thr Thr His Leu Glu Leu Gln Arg Gly Arg
 545 550 555 560

Gln Val Thr Val Pro Arg Ala Trp Leu Leu Phe Leu Arg Gly Ser Leu
565 570 575

Pro Thr Phe Arg Ser Ser Leu Phe Leu Trp Val Arg Pro Asn Gly Arg
580 585 590

Val Gly Pro Leu Val Ala Gly Arg Arg Pro Ser Ala Leu Ser Gln Gly
595 600 605

Arg Gly Gln Asp Leu Leu Ser Thr Val Ser Ile Arg Tyr Ser Gly His
610 615 620

Ser Leu
625

<210> 65
<211> 560
<212> PRT
<213> Homo sapiens

<400> 65

Met Leu Arg Gly Thr Leu Leu Cys Ala Val Leu Gly Leu Leu Arg Ala
1 5 10 15

Gln Pro Phe Pro Cys Pro Pro Ala Cys Lys Cys Val Phe Arg Asp Ala
20 25 30

Ala Gln Cys Ser Gly Gly Asp Val Ala Arg Ile Ser Ala Leu Gly Leu
35 40 45

Pro Thr Asn Leu Thr His Ile Leu Leu Phe Gly Met Gly Arg Gly Val
50 55 60

Leu Gln Ser Gln Ser Phe Ser Gly Met Thr Val Leu Gln Arg Leu Met
65 70 75 80

Ile Ser Asp Ser His Ile Ser Ala Val Ala Pro Gly Thr Phe Ser Asp
85 90 95

Leu Ile Lys Leu Lys Thr Leu Arg Leu Ser Arg Asn Lys Ile Thr His
100 105 110

Leu Pro Gly Ala Leu Leu Asp Lys Met Val Leu Leu Glu Gln Leu Phe
115 120 125

Leu Asp His Asn Ala Leu Arg Gly Ile Asp Gln Asn Met Phe Gln Lys
130 135 140

Leu Val Asn Leu Gln Glu Leu Ala Leu Asn Gln Asn Gln Leu Asp Phe
 145 150 155 160

Leu Pro Ala Ser Leu Phe Thr Asn Leu Glu Asn Leu Lys Leu Leu Asp
 165 170 175

Leu Ser Gly Asn Asn Leu Thr His Leu Pro Lys Gly Leu Leu Gly Ala
 180 185 190

Gln Ala Lys Leu Glu Arg Leu Leu Leu His Ser Asn Arg Leu Val Ser
 195 200 205

Leu Asp Ser Gly Leu Leu Asn Ser Leu Gly Ala Leu Thr Glu Leu Gln
 210 215 220

Phe His Arg Asn His Ile Arg Ser Ile Ala Pro Gly Ala Phe Asp Arg
 225 230 235 240

Leu Pro Asn Leu Ser Ser Leu Thr Leu Ser Arg Asn His Leu Ala Phe
 245 250 255

Leu Pro Ser Ala Leu Phe Leu His Ser His Asn Leu Thr Leu Leu Thr
 260 265 270

Leu Phe Glu Asn Pro Leu Ala Glu Leu Pro Gly Val Leu Phe Gly Glu
 275 280 285

Met Gly Gly Leu Gln Glu Leu Trp Leu Asn Arg Thr Gln Leu Arg Thr
 290 295 300

Leu Pro Ala Ala Ala Phe Arg Asn Leu Ser Arg Leu Arg Tyr Leu Gly
 305 310 315 320

Val Thr Leu Ser Pro Arg Leu Ser Ala Leu Pro Gln Gly Ala Phe Gln
 325 330 335

Gly Leu Gly Glu Leu Gln Val Leu Ala Leu His Ser Asn Gly Leu Thr
 340 345 350

Ala Leu Pro Asp Gly Leu Leu Arg Gly Leu Gly Lys Leu Arg Gln Val
 355 360 365

Ser Leu Arg Arg Asn Arg Leu Arg Ala Leu Pro Arg Ala Leu Phe Arg
 370 375 380

Asn Leu Ser Ser Leu Glu Ser Val Gln Leu Asp His Asn Gln Leu Glu
 385 390 395 400

Thr Leu Pro Gly Asp Val Phe Gly Ala Leu Pro Arg Leu Thr Glu Val
 405 410 415

Leu Leu Gly His Asn Ser Trp Arg Cys Asp Cys Gly Leu Gly Pro Phe
 420 425 430

Leu Gly Trp Leu Arg Gln His Leu Gly Leu Val Gly Gly Glu Glu Pro
 435 440 445

Pro Arg Cys Ala Gly Pro Gly Ala His Ala Gly Leu Pro Leu Trp Ala
 450 455 460

Leu Pro Gly Gly Asp Ala Glu Cys Pro Gly Pro Arg Gly Pro Pro Pro
 465 470 475 480

Arg Pro Ala Ala Asp Ser Ser Ser Glu Ala Pro Val His Pro Ala Leu
 485 490 495

Ala Pro Asn Ser Ser Glu Pro Trp Val Trp Ala Gln Pro Val Thr Thr
 500 505 510

Gly Lys Gly Gln Asp His Ser Pro Phe Trp Gly Phe Tyr Phe Leu Leu
 515 520 525

Leu Ala Val Gln Ala Met Ile Thr Val Ile Ile Val Phe Ala Met Ile
 530 535 540

Lys Ile Gly Gln Leu Phe Arg Lys Leu Ile Arg Glu Arg Ala Leu Gly
 545 550 555 560

<210> 66
 <211> 345
 <212> PRT
 <213> Homo sapiens

<400> 66

Met Lys Gly Glu Leu Leu Leu Phe Ser Ser Val Ile Val Leu Leu Gln
 1 5 10 15

Val Val Cys Ser Cys Pro Asp Lys Cys Tyr Cys Gln Ser Ser Thr Asn
 20 25 30

Phe Val Asp Cys Ser Gln Gln Gly Leu Ala Glu Ile Pro Ser His Leu
 35 40 45

Pro Pro Gln Thr Arg Thr Leu His Leu Gln Asp Asn Gln Ile His His
 50 55 60

Leu Pro Ala Phe Ala Phe Arg Ser Val Pro Trp Leu Met Thr Leu Asn
 65 70 75 80

Leu Ser Asn Asn Ser Leu Ser Asn Leu Ala Pro Gly Ala Phe His Gly
 85 90 95

Leu Gln His Leu Gln Val Leu Asn Leu Thr Gln Asn Ser Leu Leu Ser
 100 105 110

Leu Glu Ser Arg Leu Phe His Ser Leu Pro Gln Leu Arg Glu Leu Asp
 115 120 125

Leu Ser Ser Asn Asn Ile Ser His Leu Pro Thr Ser Leu Gly Glu Thr
 130 135 140

Trp Glu Asn Leu Thr Ile Leu Ala Val Gln Gln Asn Gln Leu Gln Gln
 145 150 155 160

Leu Asp Arg Ala Leu Leu Glu Ser Met Pro Ser Val Arg Leu Leu Leu
 165 170 175

Leu Lys Asp Asn Leu Trp Lys Cys Asn Cys His Leu Leu Gly Leu Lys
 180 185 190

Leu Trp Leu Glu Lys Phe Val Tyr Lys Gly Gly Leu Thr Asp Gly Ile
 195 200 205

Ile Cys Glu Ser Pro Asp Thr Trp Lys Gly Lys Asp Leu Leu Arg Ile
 210 215 220

Pro His Glu Leu Tyr Gln Pro Cys Pro Leu Pro Ala Pro Asp Pro Val
 225 230 235 240

Ser Ser Gln Ala Gln Trp Pro Gly Ser Ala His Gly Val Val Leu Arg
 245 250 255

Pro Pro Glu Asn His Asn Ala Gly Glu Arg Glu Leu Leu Glu Cys Glu
 260 265 270

Leu Lys Pro Lys Pro Arg Pro Ala Asn Leu Arg His Ala Ile Ala Thr
 275 280 285

Val Ile Ile Thr Gly Val Val Cys Gly Ile Val Cys Leu Met Met Leu

290 295 300
 Ala Ala Ala Ile Tyr Gly Cys Thr Tyr Ala Ala Ile Thr Ala Gln Tyr
 305 310 315 320
 His Gly Gly Pro Leu Ala Gln Thr Asn Asp Pro Gly Lys Val Glu Glu
 325 330 335
 Lys Glu Arg Phe Asp Ser Ser Pro Ala
 340 345
 <210> 67
 <211> 516
 <212> PRT
 <213> Homo sapiens
 <400> 67
 Met Gly Leu His Phe Lys Trp Pro Leu Gly Ala Pro Met Leu Ala Ala
 1 5 10 15
 Ile Tyr Ala Met Ser Met Val Leu Lys Met Leu Pro Ala Leu Gly Met
 20 25 30
 Ala Cys Pro Pro Lys Cys Arg Cys Glu Lys Leu Leu Phe Tyr Cys Asp
 35 40 45
 Ser Gln Gly Phe His Ser Val Pro Asn Ala Thr Asp Lys Gly Ser Leu
 50 55 60
 Gly Leu Ser Leu Arg His Asn His Ile Thr Glu Leu Glu Arg Asp Gln
 65 70 75 80
 Phe Ala Ser Phe Ser Gln Leu Thr Trp Leu His Leu Asp His Asn Gln
 85 90 95
 Ile Ser Thr Val Lys Glu Asp Ala Phe Gln Gly Leu Tyr Lys Leu Lys
 100 105 110
 Glu Leu Ile Leu Ser Ser Asn Lys Ile Phe Tyr Leu Pro Asn Thr Thr
 115 120 125
 Phe Thr Gln Leu Ile Asn Leu Gln Asn Leu Asp Leu Ser Phe Asn Gln
 130 135 140
 Leu Ser Ser Leu His Pro Glu Leu Phe Tyr Gly Leu Arg Lys Leu Gln
 145 150 155 160

Thr Leu His Leu Arg Ser Asn Ser Leu Arg Thr Ile Pro Val Arg Leu
 165 170 175

Phe Trp Asp Cys Arg Ser Leu Glu Phe Leu Asp Leu Ser Thr Asn Arg
 180 185 190

Leu Arg Ser Leu Ala Arg Asn Gly Phe Ala Gly Leu Ile Lys Leu Arg
 195 200 205

Glu Leu His Leu Glu His Asn Gln Leu Thr Lys Ile Asn Phe Ala His
 210 215 220

Phe Leu Arg Leu Ser Ser Leu His Thr Leu Phe Leu Gln Trp Asn Lys
 225 230 235 240

Ile Ser Asn Leu Thr Cys Gly Met Glu Trp Thr Trp Gly Thr Leu Glu
 245 250 255

Lys Leu Asp Leu Thr Gly Asn Glu Ile Lys Ala Ile Asp Leu Thr Val
 260 265 270

Phe Glu Thr Met Pro Asn Leu Lys Ile Leu Leu Met Asp Asn Asn Lys
 275 280 285

Leu Asn Ser Leu Asp Ser Lys Ile Leu Asn Ser Leu Arg Ser Leu Thr
 290 295 300

Thr Val Gly Leu Ser Gly Asn Leu Trp Glu Cys Ser Ala Arg Ile Cys
 305 310 315 320

Ala Leu Ala Ser Trp Leu Gly Ser Phe Gln Gly Arg Trp Glu His Ser
 325 330 335

Ile Leu Cys His Ser Pro Asp His Thr Gln Gly Glu Asp Ile Leu Asp
 340 345 350

Ala Val His Gly Phe Gln Leu Cys Trp Asn Leu Ser Thr Thr Val Thr
 355 360 365

Val Met Ala Thr Thr Tyr Arg Asp Pro Thr Thr Glu Tyr Thr Lys Arg
 370 375 380

Ile Ser Ser Ser Ser Tyr His Val Gly Asp Lys Glu Ile Pro Thr Thr
 385 390 395 400

Ala Gly Ile Ala Val Thr Thr Glu Glu His Phe Pro Glu Pro Asp Asn
 405 410 415

Ala Ile Phe Thr Gln Arg Val Ile Thr Gly Thr Met Ala Leu Leu Phe
 420 425 430

Ser Phe Phe Phe Ile Ile Phe Ile Val Phe Ile Ser Arg Lys Cys Cys
 435 440 445

Pro Pro Thr Leu Arg Arg Ile Arg Gln Cys Ser Met Val Gln Asn His
 450 455 460

Arg Gln Leu Arg Ser Gln Thr Arg Leu His Met Ser Asn Met Ser Asp
 465 470 475 480

Gln Gly Pro Tyr Asn Glu Tyr Glu Pro Thr His Glu Gly Pro Phe Ile
 485 490 495

Ile Ile Asn Gly Tyr Gly Gln Cys Lys Cys Gln Gln Leu Pro Tyr Lys
 500 505 510

Glu Cys Glu Val
 515

<210> 68
 <211> 661
 <212> PRT
 <213> Homo sapiens

<400> 68

Met Ala Phe Asp Val Ser Cys Phe Phe Trp Val Val Leu Phe Ser Ala
 1 5 10 15

Gly Cys Lys Val Ile Thr Ser Trp Asp Gln Met Cys Ile Glu Lys Glu
 20 25 30

Ala Asn Lys Thr Tyr Asn Cys Glu Asn Leu Gly Leu Ser Glu Ile Pro
 35 40 45

Asp Thr Leu Pro Asn Thr Thr Glu Phe Leu Glu Phe Ser Phe Asn Phe
 50 55 60

Leu Pro Thr Ile His Asn Arg Thr Phe Ser Arg Leu Met Asn Leu Thr
 65 70 75 80

Phe Leu Asp Leu Thr Arg Cys Gln Ile Asn Trp Ile His Glu Asp Thr
 85 90 95

Phe Gln Ser His His Gln Leu Ser Thr Leu Val Leu Thr Gly Asn Pro

100	105	110
Leu Ile Phe Met Ala Glu Thr Ser Leu Asn Gly Pro Lys Ser Leu Lys		
115	120	125
His Leu Phe Leu Ile Gln Thr Gly Ile Ser Asn Leu Glu Phe Ile Pro		
130	135	140
Val His Asn Leu Glu Asn Leu Glu Ser Leu Tyr Leu Gly Ser Asn His		
145	150	155
Ile Ser Ser Ile Lys Phe Pro Lys Asp Phe Pro Ala Arg Asn Leu Lys		
165	170	175
Val Leu Asp Phe Gln Asn Asn Ala Ile His Tyr Ile Ser Arg Glu Asp		
180	185	190
Met Arg Ser Leu Glu Gln Ala Ile Asn Leu Ser Leu Asn Phe Asn Gly		
195	200	205
Asn Asn Val Lys Gly Ile Glu Leu Gly Ala Phe Asp Ser Thr Ile Phe		
210	215	220
Gln Ser Leu Asn Phe Gly Gly Thr Pro Asn Leu Ser Val Ile Phe Asn		
225	230	235
Gly Leu Gln Asn Ser Thr Thr Gln Ser Leu Trp Leu Gly Thr Phe Glu		
245	250	255
Asp Ile Asp Asp Glu Asp Ile Ser Ser Ala Met Leu Lys Gly Leu Cys		
260	265	270
Glu Met Ser Val Glu Ser Leu Asn Leu Gln Glu His Arg Phe Ser Asp		
275	280	285
Ile Ser Ser Thr Thr Phe Gln Cys Phe Thr Gln Leu Gln Glu Leu Asp		
290	295	300
Leu Thr Ala Thr His Leu Lys Gly Leu Pro Ser Gly Met Lys Gly Leu		
305	310	315
Asn Leu Leu Lys Lys Leu Val Leu Ser Val Asn His Phe Asp Gln Leu		
325	330	335
Cys Gln Ile Ser Ala Ala Asn Phe Pro Ser Leu Thr His Leu Tyr Ile		
340	345	350

Arg Gly Asn Val Lys Lys Leu His Leu Gly Val Gly Cys Leu Glu Lys
 355 360 365

Leu Gly Asn Leu Gln Thr Leu Asp Leu Ser His Asn Asp Ile Glu Ala
 370 375 380

Ser Asp Cys Cys Ser Leu Gln Leu Lys Asn Leu Ser His Leu Gln Thr
 385 390 395 400

Leu Asn Leu Ser His Asn Glu Pro Leu Gly Leu Gln Ser Gln Ala Phe
 405 410 415

Lys Glu Cys Pro Gln Leu Glu Leu Leu Asp Leu Ala Phe Thr Arg Leu
 420 425 430

His Ile Asn Ala Pro Gln Ser Pro Phe Gln Asn Leu His Phe Leu Gln
 435 440 445

Val Leu Asn Leu Thr Tyr Cys Phe Leu Asp Thr Ser Asn Gln His Leu
 450 455 460

Leu Ala Gly Leu Pro Val Leu Arg His Leu Asn Leu Lys Gly Asn His
 465 470 475 480

Phe Gln Asp Gly Thr Ile Thr Lys Thr Asn Leu Leu Gln Thr Val Gly
 485 490 495

Ser Leu Glu Val Leu Ile Leu Ser Ser Cys Gly Leu Leu Ser Ile Asp
 500 505 510

Gln Gln Ala Phe His Ser Leu Gly Lys Met Ser His Val Asp Leu Ser
 515 520 525

His Asn Ser Leu Thr Cys Asp Ser Ile Asp Ser Leu Ser His Leu Lys
 530 535 540

Gly Ile Tyr Leu Asn Leu Ala Ala Asn Ser Ile Asn Ile Ile Ser Pro
 545 550 555 560

Arg Leu Leu Pro Ile Leu Ser Gln Gln Ser Thr Ile Asn Leu Ser His
 565 570 575

Asn Pro Leu Asp Cys Thr Cys Ser Asn Ile His Phe Leu Thr Trp Tyr
 580 585 590

Lys Glu Asn Leu His Lys Leu Glu Gly Ser Glu Glu Thr Thr Cys Ala

595	600	605
Asn Pro Pro Ser Leu Arg Gly Val Lys Leu Ser Asp Val Lys Leu Ser		
610	615	620
Cys Gly Ile Thr Ala Ile Gly Ile Phe Phe Leu Ile Val Phe Leu Leu		
625	630	635
Leu Leu Ala Ile Leu Leu Phe Phe Ala Val Lys Tyr Leu Leu Arg Trp		
	645	650
		655
Lys Tyr Gln His Ile		
	660	
<210> 69		
<211> 614		
<212> PRT		
<213> Homo sapiens		
<400> 69		
Met Leu Ala Gly Gly Val Arg Ser Met Pro Ser Pro Leu Leu Ala Cys		
1	5	10
		15
Trp Gln Pro Ile Leu Leu Leu Val Leu Gly Ser Val Leu Ser Gly Ser		
	20	25
		30
Ala Thr Gly Cys Pro Pro Arg Cys Glu Cys Ser Ala Gln Asp Arg Ala		
	35	40
		45
Val Leu Cys His Arg Lys Arg Phe Val Ala Val Pro Glu Gly Ile Pro		
	50	55
		60
Thr Glu Thr Arg Leu Leu Asp Leu Gly Lys Asn Arg Ile Lys Thr Leu		
65	70	75
		80
Asn Gln Asp Glu Phe Ala Ser Phe Pro His Leu Glu Glu Leu Glu Leu		
	85	90
		95
Asn Glu Asn Ile Val Ser Ala Val Glu Pro Gly Ala Phe Asn Asn Leu		
	100	105
		110
Phe Asn Leu Arg Thr Leu Gly Leu Arg Ser Asn Arg Leu Lys Leu Ile		
	115	120
		125
Pro Leu Gly Val Phe Thr Gly Leu Ser Asn Leu Thr Lys Leu Asp Ile		
	130	135
		140

Ser Glu Asn Lys Ile Val Ile Leu Leu Asp Tyr Met Phe Gln Asp Leu
 145 150 155 160

Tyr Asn Leu Lys Ser Leu Glu Val Gly Asp Asn Asp Leu Val Tyr Ile
 165 170 175

Ser His Arg Ala Phe Ser Gly Leu Asn Ser Leu Glu Gln Leu Thr Leu
 180 185 190

Glu Lys Cys Asn Leu Thr Ser Ile Pro Thr Glu Ala Leu Ser His Leu
 195 200 205

His Gly Leu Ile Val Leu Arg Leu Arg His Leu Asn Ile Asn Ala Ile
 210 215 220

Arg Asp Tyr Ser Phe Lys Arg Leu Tyr Arg Leu Lys Val Leu Glu Ile
 225 230 235 240

Ser His Trp Pro Tyr Leu Asp Thr Met Thr Pro Asn Cys Leu Tyr Gly
 245 250 255

Leu Asn Leu Thr Ser Leu Ser Ile Thr His Cys Asn Leu Thr Ala Val
 260 265 270

Pro Tyr Leu Ala Val Arg His Leu Val Tyr Leu Arg Phe Leu Asn Leu
 275 280 285

Ser Tyr Asn Pro Ile Ser Thr Ile Glu Gly Ser Met Leu His Glu Leu
 290 295 300

Leu Arg Leu Gln Glu Ile Gln Leu Val Gly Gly Gln Leu Ala Val Val
 305 310 315 320

Glu Pro Tyr Ala Phe Arg Gly Leu Asn Tyr Leu Arg Val Leu Asn Val
 325 330 335

Ser Gly Asn Gln Leu Thr Thr Leu Glu Glu Ser Val Phe His Ser Val
 340 345 350

Gly Asn Leu Glu Thr Leu Ile Leu Asp Ser Asn Pro Leu Ala Cys Asp
 355 360 365

Cys Arg Leu Leu Trp Val Phe Arg Arg Arg Trp Arg Leu Asn Phe Asn
 370 375 380

Arg Gln Gln Pro Thr Cys Ala Thr Pro Glu Phe Val Gln Gly Lys Glu
 385 390 395 400

Phe Lys Asp Phe Pro Asp Val Leu Leu Pro Asn Tyr Phe Thr Cys Arg
 405 410 415
 Arg Ala Arg Ile Arg Asp Arg Lys Ala Gln Gln Val Phe Val Asp Glu
 420 425 430
 Gly His Thr Val Gln Phe Val Cys Arg Ala Asp Gly Asp Pro Pro Pro
 435 440 445
 Ala Ile Leu Trp Leu Ser Pro Arg Lys His Leu Val Ser Ala Lys Ser
 450 455 460
 Asn Gly Arg Leu Thr Val Phe Pro Asp Gly Thr Leu Glu Val Arg Tyr
 465 470 475 480
 Ala Gln Val Gln Asp Asn Gly Thr Tyr Leu Cys Ile Ala Ala Asn Ala
 485 490 495
 Gly Gly Asn Asp Ser Met Pro Ala His Leu His Val Arg Ser Tyr Ser
 500 505 510
 Pro Asp Trp Pro His Gln Pro Asn Lys Thr Phe Ala Phe Ile Ser Asn
 515 520 525
 Gln Pro Gly Glu Gly Glu Ala Asn Ser Thr Arg Ala Thr Val Pro Phe
 530 535 540
 Pro Phe Asp Ile Lys Thr Leu Ile Ile Ala Thr Thr Met Gly Phe Ile
 545 550 555 560
 Ser Phe Leu Gly Val Val Leu Phe Cys Leu Val Leu Leu Phe Leu Trp
 565 570 575
 Ser Arg Gly Lys Gly Asn Thr Lys His Asn Ile Glu Ile Glu Tyr Val
 580 585 590
 Pro Arg Lys Ser Asp Ala Gly Ile Ser Ser Ala Asp Ala Pro Arg Lys
 595 600 605
 Phe Asn Met Lys Met Ile
 610

<210> 70
 <211> 428
 <212> PRT
 <213> Homo sapiens

<400> 70

Met Gln Glu Leu His Leu Leu Trp Trp Ala Leu Leu Leu Gly Leu Ala
 1 5 10 15
 Gln Ala Cys Pro Glu Pro Cys Asp Cys Gly Glu Lys Tyr Gly Phe Gln
 20 25 30
 Ile Ala Asp Cys Ala Tyr Arg Asp Leu Glu Ser Val Pro Pro Gly Phe
 35 40 45
 Pro Ala Asn Val Thr Thr Leu Ser Leu Ser Ala Asn Arg Leu Pro Gly
 50 55 60
 Leu Pro Glu Gly Ala Phe Arg Glu Val Pro Leu Leu Gln Ser Leu Trp
 65 70 75 80
 Leu Ala His Asn Glu Ile Arg Thr Val Ala Ala Gly Ala Leu Ala Ser
 85 90 95
 Leu Ser His Leu Lys Ser Leu Asp Leu Ser His Asn Leu Ile Ser Asp
 100 105 110
 Phe Ala Trp Ser Asp Leu His Asn Leu Ser Ala Leu Gln Leu Leu Lys
 115 120 125
 Met Asp Ser Asn Glu Leu Thr Phe Ile Pro Arg Asp Ala Phe Arg Ser
 130 135 140
 Leu Arg Ala Leu Arg Ser Leu Gln Leu Asn His Asn Arg Leu His Thr
 145 150 155 160
 Leu Ala Glu Gly Thr Phe Thr Pro Leu Thr Ala Leu Ser His Leu Gln
 165 170 175
 Ile Asn Glu Asn Pro Phe Asp Cys Thr Cys Gly Ile Val Trp Leu Lys
 180 185 190
 Thr Trp Ala Leu Thr Thr Ala Val Ser Ile Pro Glu Gln Asp Asn Ile
 195 200 205
 Ala Cys Thr Ser Pro His Val Leu Lys Gly Thr Pro Leu Ser Arg Leu
 210 215 220
 Pro Pro Leu Pro Cys Ser Ala Pro Ser Val Gln Leu Ser Tyr Gln Pro
 225 230 235 240

Ser Gln Asp Gly Ala Glu Leu Arg Pro Gly Phe Val Leu Ala Leu His
 245 250 255

Cys Asp Val Asp Gly Gln Pro Ala Pro Gln Leu His Trp His Ile Gln
 260 265 270

Ile Pro Ser Gly Ile Val Glu Ile Thr Ser Pro Asn Val Gly Thr Asp
 275 280 285

Gly Arg Ala Leu Pro Gly Thr Pro Val Ala Ser Ser Gln Pro Arg Phe
 290 295 300

Gln Ala Phe Ala Asn Gly Ser Leu Leu Ile Pro Asp Phe Gly Lys Leu
 305 310 315 320

Glu Glu Gly Thr Tyr Ser Cys Leu Ala Thr Asn Glu Leu Gly Ser Ala
 325 330 335

Glu Ser Ser Val Asp Val Ala Leu Ala Thr Pro Gly Glu Gly Gly Glu
 340 345 350

Asp Thr Leu Gly Arg Arg Phe His Gly Lys Ala Val Glu Gly Lys Gly
 355 360 365

Cys Tyr Thr Val Asp Asn Glu Val Gln Pro Ser Gly Pro Glu Asp Asn
 370 375 380

Val Val Ile Ile Tyr Leu Ser Arg Ala Gly Asn Pro Glu Ala Ala Val
 385 390 395 400

Ala Glu Gly Val Pro Gly Gln Leu Pro Pro Gly Leu Leu Leu Leu Gly
 405 410 415

Gln Ser Leu Leu Leu Phe Phe Phe Leu Thr Ser Phe
 420 425

<210> 71
 <211> 612
 <212> PRT
 <213> Homo sapiens

<400> 71

Met Asp Val Ser Leu Cys Pro Ala Lys Cys Ser Phe Trp Arg Ile Phe
 1 5 10 15

Leu Leu Gly Ser Val Trp Leu Asp Tyr Val Gly Ser Val Leu Ala Cys
 20 25 30

Pro Ala Asn Cys Val Cys Ser Lys Thr Glu Ile Asn Cys Arg Arg Pro
 35 40 45

Asp Asp Gly Asn Leu Phe Pro Leu Leu Glu Gly Gln Asp Ser Gly Asn
 50 55 60

Ser Asn Gly Asn Ala Ser Ile Asn Ile Thr Asp Ile Ser Arg Asn Ile
 65 70 75 80

Thr Ser Ile His Ile Glu Asn Trp Arg Ser Leu His Thr Leu Asn Ala
 85 90 95

Val Asp Met Glu Leu Tyr Thr Gly Leu Gln Lys Leu Thr Ile Lys Asn
 100 105 110

Ser Gly Leu Arg Ser Ile Gln Pro Arg Ala Phe Ala Lys Asn Pro His
 115 120 125

Leu Arg Tyr Ile Asn Leu Ser Ser Asn Arg Leu Thr Thr Leu Ser Trp
 130 135 140

Gln Leu Phe Gln Thr Leu Ser Leu Arg Glu Leu Gln Leu Glu Gln Asn
 145 150 155 160

Phe Phe Asn Cys Ser Cys Asp Ile Arg Trp Met Gln Leu Trp Gln Glu
 165 170 175

Gln Gly Glu Ala Lys Leu Asn Ser Gln Asn Leu Tyr Cys Ile Asn Ala
 180 185 190

Asp Gly Ser Gln Leu Pro Leu Phe Arg Met Asn Ile Ser Gln Cys Asp
 195 200 205

Leu Pro Glu Ile Ser Val Ser His Val Asn Leu Thr Val Arg Glu Gly
 210 215 220

Asp Asn Ala Val Ile Thr Cys Asn Gly Ser Gly Ser Pro Leu Pro Asp
 225 230 235 240

Val Asp Trp Ile Val Thr Gly Leu Gln Ser Ile Asn Thr His Gln Thr
 245 250 255

Asn Leu Asn Trp Thr Asn Val His Ala Ile Asn Leu Thr Leu Val Asn
 260 265 270

Val Thr Ser Glu Asp Asn Gly Phe Thr Leu Thr Cys Ile Ala Glu Asn
 275 280 285

Val Val Gly Met Ser Asn Ala Ser Val Ala Leu Thr Val Tyr Tyr Pro
 290 295 300

Pro Arg Val Val Ser Leu Glu Glu Pro Glu Leu Arg Leu Glu His Cys
 305 310 315 320

Ile Glu Phe Val Val Arg Gly Asn Pro Pro Pro Thr Leu His Trp Leu
 325 330 335

His Asn Gly Gln Pro Leu Arg Glu Ser Lys Ile Ile His Val Glu Tyr
 340 345 350

Tyr Gln Glu Gly Glu Ile Ser Glu Gly Cys Leu Leu Phe Asn Lys Pro
 355 360 365

Thr His Tyr Asn Asn Gly Asn Tyr Thr Leu Ile Ala Lys Asn Pro Leu
 370 375 380

Gly Thr Ala Asn Gln Thr Ile Asn Gly His Phe Leu Lys Glu Pro Phe
 385 390 395 400

Pro Glu Ser Thr Asp Asn Phe Ile Leu Phe Asp Glu Val Ser Pro Thr
 405 410 415

Pro Pro Ile Thr Val Thr His Lys Pro Glu Glu Asp Thr Phe Gly Val
 420 425 430

Ser Ile Ala Val Gly Leu Ala Ala Phe Ala Cys Val Leu Leu Val Val
 435 440 445

Leu Phe Val Met Ile Asn Lys Tyr Gly Arg Arg Ser Lys Phe Gly Met
 450 455 460

Lys Gly Pro Val Ala Val Ile Ser Gly Glu Glu Asp Ser Ala Ser Pro
 465 470 475 480

Leu His His Ile Asn His Gly Ile Thr Thr Pro Ser Ser Leu Asp Ala
 485 490 495

Gly Pro Asp Thr Val Val Ile Gly Met Thr Arg Ile Pro Val Ile Glu
 500 505 510

Asn Pro Gln Tyr Phe Arg Gln Gly His Asn Cys His Lys Pro Asp Thr
 515 520 525

Trp Val Phe Ser Asn Ile Asp Asn His Gly Ile Leu Asn Leu Lys Asp
 530 535 540

Asn Arg Asp His Leu Val Pro Ser Thr His Tyr Ile Tyr Glu Glu Pro
 545 550 555 560

Glu Val Gln Ser Gly Glu Val Ser Tyr Pro Arg Ser His Gly Phe Arg
 565 570 575

Glu Ile Met Leu Asn Pro Ile Ser Leu Pro Gly His Ser Lys Pro Leu
 580 585 590

Asn His Gly Ile Tyr Val Glu Asp Val Asn Val Tyr Phe Ser Lys Gly
 595 600 605

Arg His Gly Phe
 610

<210> 72
 <211> 493
 <212> PRT
 <213> Homo sapiens

<400> 72

Met His Pro His Arg Asp Pro Arg Gly Leu Trp Leu Leu Leu Pro Ser
 1 5 10 15

Leu Ser Leu Leu Leu Phe Glu Val Ala Arg Ala Gly Arg Ala Val Val
 20 25 30

Ser Cys Pro Ala Ala Cys Leu Cys Ala Ser Asn Ile Leu Ser Cys Ser
 35 40 45

Lys Gln Gln Leu Pro Asn Val Pro His Ser Leu Pro Ser Tyr Thr Ala
 50 55 60

Leu Leu Asp Leu Ser His Asn Asn Leu Ser Arg Leu Arg Ala Glu Trp
 65 70 75 80

Thr Pro Thr Arg Leu Thr Gln Leu His Ser Leu Leu Leu Ser His Asn
 85 90 95

His Leu Asn Phe Ile Ser Ser Glu Ala Phe Ser Pro Val Pro Asn Leu
 100 105 110

Arg Tyr Leu Asp Leu Ser Ser Asn Gln Leu Arg Thr Leu Asp Glu Phe

115	120	125
Leu Phe Ser Asp Leu Gln Val Leu Glu Val Leu Leu Leu Tyr Asn Asn		
130	135	140
His Ile Met Ala Val Asp Arg Cys Ala Phe Asp Asp Met Ala Gln Leu		
145	150	155
Gln Lys Leu Tyr Leu Ser Gln Asn Gln Ile Ser Arg Phe Pro Leu Glu		
	165	170
Leu Val Lys Glu Gly Ala Lys Leu Pro Lys Leu Thr Leu Leu Asp Leu		
	180	185
Ser Ser Asn Lys Leu Lys Asn Leu Pro Leu Pro Asp Leu Gln Lys Leu		
	195	200
Pro Ala Trp Ile Lys Asn Gly Leu Tyr Leu His Asn Asn Pro Leu Asn		
	210	215
Cys Asp Cys Glu Leu Tyr Gln Leu Phe Ser His Trp Gln Tyr Arg Gln		
225	230	235
Leu Ser Ser Val Met Asp Phe Gln Glu Asp Leu Tyr Cys Met Asn Ser		
	245	250
Lys Lys Leu His Asn Val Phe Asn Leu Ser Phe Leu Asn Cys Gly Glu		
	260	265
Tyr Lys Glu Arg Ala Trp Glu Ala His Leu Gly Asp Thr Leu Ile Ile		
	275	280
Lys Cys Asp Thr Lys Gln Gln Gly Met Thr Lys Val Trp Val Thr Pro		
	290	295
Ser Asn Glu Arg Val Leu Asp Glu Val Thr Asn Gly Thr Val Ser Val		
305	310	315
Ser Lys Asp Gly Ser Leu Leu Phe Gln Gln Val Gln Val Glu Asp Gly		
	325	330
Gly Val Tyr Thr Cys Tyr Ala Met Gly Glu Thr Phe Asn Glu Thr Leu		
	340	345
Ser Val Glu Leu Lys Val His Asn Phe Thr Leu His Gly His His Asp		
	355	360

Thr Leu Asn Thr Ala Tyr Thr Thr Leu Val Gly Cys Ile Leu Ser Val
 370 375 380

Val Leu Val Leu Ile Tyr Leu Tyr Leu Thr Pro Cys Arg Cys Trp Cys
 385 390 395 400

Arg Gly Val Glu Lys Pro Ser Ser His Gln Gly Asp Ser Leu Ser Ser
 405 410 415

Ser Met Leu Ser Thr Thr Pro Asn His Asp Pro Met Ala Gly Gly Asp
 420 425 430

Lys Asp Asp Gly Phe Asp Arg Arg Val Ala Phe Leu Glu Pro Ala Gly
 435 440 445

Pro Gly Gln Gly Gln Asn Gly Lys Leu Lys Pro Gly Asn Thr Leu Pro
 450 455 460

Val Pro Glu Ala Thr Gly Lys Gly Gln Arg Arg Met Ser Asp Pro Glu
 465 470 475 480

Ser Val Ser Ser Val Phe Ser Asp Thr Pro Ile Val Val
 485 490

<210> 73
 <211> 616
 <212> PRT
 <213> Homo sapiens

<400> 73

Met Asn His Asn Arg Leu Gly Ser Leu Pro Arg Asp Ala Leu Gly Ala
 1 5 10 15

Leu Pro Asp Leu Arg Ser Leu Arg Ile Asn Asn Asn Arg Leu Arg Thr
 20 25 30

Leu Ala Pro Gly Thr Phe Asp Ala Leu Ser Ala Leu Ser His Leu Gln
 35 40 45

Leu Tyr His Asn Pro Phe His Cys Gly Cys Gly Leu Val Trp Leu Gln
 50 55 60

Ala Trp Ala Ala Ser Thr Arg Val Ser Leu Pro Glu Pro Asp Ser Ile
 65 70 75 80

Ala Cys Ala Ser Pro Pro Ala Leu Gln Gly Val Pro Val Tyr Arg Leu
 85 90 95

Pro Ala Leu Pro Cys Ala Pro Pro Ser Val His Leu Ser Ala Glu Pro
 100 105 110

Pro Leu Glu Ala Pro Gly Thr Pro Leu Arg Ala Gly Leu Ala Phe Val
 115 120 125

Leu His Cys Ile Ala Asp Gly His Pro Thr Pro Arg Leu Gln Trp Gln
 130 135 140

Leu Gln Ile Pro Gly Gly Thr Val Val Leu Glu Pro Pro Val Leu Ser
 145 150 155 160

Gly Glu Asp Asp Gly Val Gly Ala Glu Glu Gly Glu Gly Glu Gly Asp
 165 170 175

Gly Asp Leu Leu Thr Gln Thr Gln Ala Gln Thr Pro Thr Pro Ala Pro
 180 185 190

Ala Trp Pro Ala Pro Pro Ala Thr Pro Arg Phe Leu Ala Leu Ala Asn
 195 200 205

Gly Ser Leu Leu Val Pro Leu Leu Ser Ala Lys Glu Ala Gly Val Tyr
 210 215 220

Thr Cys Arg Ala His Asn Glu Leu Gly Ala Asn Ser Thr Ser Ile Arg
 225 230 235 240

Val Ala Val Ala Ala Thr Gly Pro Pro Lys His Ala Pro Gly Ala Gly
 245 250 255

Gly Glu Pro Asp Gly Gln Ala Pro Thr Ser Glu Arg Lys Ser Thr Ala
 260 265 270

Lys Gly Arg Gly Asn Ser Val Leu Pro Ser Lys Pro Glu Gly Lys Ile
 275 280 285

Lys Gly Gln Gly Leu Ala Lys Val Ser Ile Leu Gly Glu Thr Glu Thr
 290 295 300

Glu Pro Glu Glu Asp Thr Ser Glu Gly Glu Glu Ala Glu Asp Gln Ile
 305 310 315 320

Leu Ala Asp Pro Ala Glu Glu Gln Arg Cys Gly Asn Gly Asp Pro Ser
 325 330 335

Arg Tyr Val Ser Asn His Ala Phe Asn Gln Ser Ala Glu Leu Lys Pro
 340 345 350

His Val Phe Glu Leu Gly Val Ile Ala Leu Asp Val Ala Glu Arg Glu
 355 360 365

Ala Arg Val Gln Leu Thr Pro Leu Ala Ala Arg Trp Gly Pro Gly Pro
 370 375 380

Gly Gly Ala Gly Gly Ala Pro Arg Pro Gly Arg Arg Pro Leu Arg Leu
 385 390 395 400

Leu Tyr Leu Cys Pro Ala Gly Gly Gly Ala Ala Val Gln Trp Ser Arg
 405 410 415

Val Glu Glu Gly Val Asn Ala Tyr Trp Phe Arg Gly Leu Arg Pro Gly
 420 425 430

Thr Asn Tyr Ser Val Cys Leu Ala Leu Ala Gly Glu Ala Cys His Val
 435 440 445

Gln Val Val Phe Ser Thr Lys Lys Glu Leu Pro Ser Leu Leu Val Ile
 450 455 460

Val Ala Val Ser Val Phe Leu Leu Val Leu Ala Thr Val Pro Leu Leu
 465 470 475 480

Gly Ala Ala Cys Cys His Leu Leu Ala Lys His Pro Gly Lys Pro Tyr
 485 490 495

Arg Leu Ile Leu Arg Pro Gln Ala Pro Asp Pro Met Glu Lys Arg Ile
 500 505 510

Ala Ala Asp Phe Asp Pro Arg Ala Ser Tyr Leu Glu Ser Glu Lys Ser
 515 520 525

Tyr Pro Ala Gly Gly Glu Ala Gly Gly Glu Glu Pro Glu Asp Val Gln
 530 535 540

Gly Glu Gly Leu Asp Glu Asp Ala Glu Gln Gly Asp Pro Ser Gly Asp
 545 550 555 560

Leu Gln Arg Glu Glu Ser Leu Ala Ala Cys Ser Leu Val Glu Ser Gln
 565 570 575

Ser Lys Ala Asn Gln Glu Glu Phe Glu Ala Gly Ser Glu Tyr Ser Asp
 580 585 590

Arg Leu Pro Leu Gly Ala Glu Ala Val Asn Ile Ala Gln Glu Ile Asn
 595 600 605

Gly Asn Tyr Arg Gln Thr Ala Gly
 610 615

<210> 74
 <211> 504
 <212> PRT
 <213> Homo sapiens

<400> 74

Met Thr Trp Leu Val Leu Leu Gly Thr Leu Leu Cys Met Leu Arg Val
 1 5 10 15

Gly Leu Gly Thr Pro Asp Ser Glu Gly Phe Pro Pro Arg Ala Leu His
 20 25 30

Asn Cys Pro Tyr Lys Cys Ile Cys Ala Ala Asp Leu Leu Ser Cys Thr
 35 40 45

Gly Leu Gly Leu Gln Asp Val Pro Ala Glu Leu Pro Ala Ala Thr Ala
 50 55 60

Asp Leu Asp Leu Ser His Asn Ala Leu Gln Arg Leu Arg Pro Gly Trp
 65 70 75 80

Leu Ala Pro Leu Phe Gln Leu Arg Ala Leu His Leu Asp His Asn Glu
 85 90 95

Leu Asp Ala Leu Gly Arg Gly Val Phe Val Asn Ala Ser Gly Leu Arg
 100 105 110

Leu Leu Asp Leu Ser Ser Asn Thr Leu Arg Ala Leu Gly Arg His Asp
 115 120 125

Leu Asp Gly Leu Gly Ala Leu Glu Lys Leu Leu Leu Phe Asn Asn Arg
 130 135 140

Leu Val His Leu Asp Glu His Ala Phe His Gly Leu Arg Ala Leu Ser
 145 150 155 160

His Leu Tyr Leu Gly Cys Asn Glu Leu Ala Ser Phe Ser Phe Asp His
 165 170 175

Leu His Gly Leu Ser Ala Thr His Leu Leu Thr Leu Asp Leu Ser Ser

180	185	190
Asn Arg Leu Gly His Ile Ser Val Pro Glu Leu Ala Ala Leu Pro Ala 195 200 205		
Phe Leu Lys Asn Gly Leu Tyr Leu His Asn Asn Pro Leu Pro Cys Asp 210 215 220		
Cys Arg Leu Tyr His Leu Leu Gln Arg Trp His Gln Arg Gly Leu Ser 225 230 235 240		
Ala Val Arg Asp Phe Ala Arg Glu Tyr Val Cys Leu Ala Phe Lys Val 245 250 255		
Pro Ala Ser Arg Val Arg Phe Phe Gln His Ser Arg Val Phe Glu Asn 260 265 270		
Cys Ser Ser Ala Pro Ala Leu Gly Leu Glu Arg Pro Glu Glu His Leu 275 280 285		
Tyr Ala Leu Val Gly Arg Ser Leu Arg Leu Tyr Cys Asn Thr Ser Val 290 295 300		
Pro Ala Met Arg Ile Ala Trp Val Ser Pro Gln Gln Glu Leu Leu Arg 305 310 315 320		
Ala Pro Gly Ser Arg Asp Gly Ser Ile Ala Val Leu Ala Asp Gly Ser 325 330 335		
Leu Ala Ile Gly Asn Val Gln Glu Gln His Ala Gly Leu Phe Val Cys 340 345 350		
Leu Ala Thr Gly Pro Arg Leu His His Asn Gln Thr His Glu Tyr Asn 355 360 365		
Val Ser Val His Phe Pro Arg Pro Glu Pro Glu Ala Phe Asn Thr Gly 370 375 380		
Phe Thr Thr Leu Leu Gly Cys Ala Val Gly Leu Val Leu Val Leu Leu 385 390 395 400		
Tyr Leu Phe Ala Pro Pro Cys Arg Cys Cys Arg Arg Ala Cys Arg Cys 405 410 415		
Arg Arg Trp Pro Gln Thr Pro Ser Pro Leu Gln Glu Leu Ser Ala Gln 420 425 430		

Ser Ser Val Leu Ser Thr Thr Pro Pro Asp Ala Pro Ser Arg Lys Ala
 435 440 445

Ser Val His Lys His Val Val Phe Leu Glu Pro Gly Arg Arg Gly Leu
 450 455 460

Asn Gly Arg Val Gln Leu Ala Val Ala Glu Glu Phe Asp Leu Tyr Asn
 465 470 475 480

Pro Gly Gly Leu Gln Leu Lys Ala Gly Ser Glu Ser Ala Ser Ser Ile
 485 490 495

Gly Ser Glu Gly Pro Met Thr Thr
 500

<210> 75
 <211> 623
 <212> PRT
 <213> Homo sapiens

<400> 75

Met Arg Val Ala Leu Gly Met Leu Trp Leu Leu Ala Leu Ala Trp Pro
 1 5 10 15

Pro Gln Ala Arg Gly Phe Cys Pro Ser Gln Cys Ser Cys Ser Leu His
 20 25 30

Ile Met Gly Asp Gly Ser Lys Ala Arg Thr Val Val Cys Asn Asp Pro
 35 40 45

Asp Met Thr Leu Pro Pro Ala Ser Ile Pro Pro Asp Thr Ser Arg Leu
 50 55 60

Arg Leu Glu Arg Thr Ala Ile Arg Arg Val Pro Gly Glu Ala Phe Arg
 65 70 75 80

Pro Leu Gly Arg Leu Glu Gln Leu Trp Leu Pro Tyr Asn Ala Leu Ser
 85 90 95

Glu Leu Asn Ala Leu Met Leu Arg Gly Leu Arg Arg Leu Arg Glu Leu
 100 105 110

Arg Leu Pro Gly Asn Arg Leu Ala Ala Phe Pro Trp Ala Ala Leu Arg
 115 120 125

Asp Ala Pro Lys Leu Arg Leu Leu Asp Leu Gln Ala Asn Arg Leu Ser
 130 135 140

Ala Val Pro Ala Glu Ala Ala Arg Phe Leu Glu Asn Leu Thr Phe Leu
 145 150 155 160

Asp Leu Ser Ser Asn Gln Leu Met Arg Leu Pro Gln Glu Leu Ile Val
 165 170 175

Ser Trp Ala His Leu Glu Thr Gly Ile Phe Pro Pro Gly His His Pro
 180 185 190

Arg Arg Val Leu Gly Leu Gln Asp Asn Pro Trp Ala Cys Asp Cys Arg
 195 200 205

Leu Tyr Asp Leu Val His Leu Leu Asp Gly Trp Ala Pro Asn Leu Ala
 210 215 220

Phe Ile Glu Thr Glu Leu Arg Cys Ala Ser Pro Arg Ser Leu Ala Gly
 225 230 235 240

Val Ala Phe Ser Gln Leu Glu Leu Arg Lys Cys Gln Gly Pro Glu Leu
 245 250 255

His Pro Gly Val Ala Ser Ile Arg Ser Leu Leu Gly Gly Thr Ala Leu
 260 265 270

Leu Arg Cys Gly Ala Thr Gly Val Pro Gly Pro Glu Met Ser Trp Arg
 275 280 285

Arg Ala Asn Gly Arg Pro Leu Asn Gly Thr Val His Gln Glu Val Ser
 290 295 300

Ser Asp Gly Thr Ser Trp Thr Leu Leu Gly Leu Pro Ala Val Ser His
 305 310 315 320

Leu Asp Ser Gly Asp Tyr Ile Cys Gln Ala Lys Asn Phe Leu Gly Ala
 325 330 335

Ser Glu Thr Val Ile Ser Leu Ile Val Thr Glu Pro Pro Thr Ser Thr
 340 345 350

Glu His Ser Gly Ser Pro Gly Ala Leu Trp Ala Arg Thr Gly Gly Gly
 355 360 365

Gly Glu Ala Ala Ala Tyr Asn Asn Lys Leu Val Ala Arg His Val Pro
 370 375 380

Gln Ile Pro Lys Pro Ala Val Leu Ala Thr Gly Pro Ser Val Pro Ser
385 390 395 400

Thr Lys Glu Glu Leu Thr Leu Glu His Phe Gln Met Asp Ala Leu Gly
405 410 415

Glu Leu Ser Asp Gly Arg Ala Gly Pro Ser Glu Ala Arg Met Val Arg
420 425 430

Ser Val Lys Val Val Gly Asp Thr Tyr His Ser Val Ser Leu Val Trp
435 440 445

Lys Ala Pro Gln Ala Lys Asn Thr Thr Ala Phe Ser Val Leu Tyr Ala
450 455 460

Val Phe Gly Gln His Ser Met Arg Arg Val Ile Val Gln Pro Gly Lys
465 470 475 480

Thr Arg Val Thr Ile Thr Gly Leu Leu Pro Lys Thr Lys Tyr Val Ala
485 490 495

Cys Val Cys Val Gln Gly Leu Val Pro Arg Lys Glu Gln Cys Val Ile
500 505 510

Phe Ser Thr Asn Glu Val Val Asp Ala Glu Asn Thr Gln Gln Leu Ile
515 520 525

Asn Val Val Val Ile Ser Val Ala Ile Val Ile Ala Leu Pro Leu Thr
530 535 540

Leu Leu Val Cys Cys Ser Ala Leu Gln Lys Arg Cys Arg Lys Cys Phe
545 550 555 560

Asn Lys Asp Ser Thr Glu Ala Thr Val Thr Tyr Val Asn Leu Glu Arg
565 570 575

Leu Gly Tyr Ser Glu Asp Gly Leu Glu Glu Leu Ser Arg His Ser Val
580 585 590

Ser Glu Ala Asp Arg Leu Leu Ser Ala Arg Ser Ser Val Asp Phe Gln
595 600 605

Ala Phe Gly Val Lys Gly Gly Arg Arg Ile Asn Glu Tyr Phe Cys
610 615 620

<210> 76
<211> 789

<212> PRT

<213> Homo sapiens

<400> 76

Met Glu Thr Leu Leu Gly Gly Leu Leu Ala Phe Gly Met Ala Phe Ala
 1 5 10 15

Val Val Asp Ala Cys Pro Lys Tyr Cys Val Cys Gln Asn Leu Ser Glu
 20 25 30

Ser Leu Gly Thr Leu Cys Pro Ser Lys Gly Leu Leu Phe Val Pro Pro
 35 40 45

Asp Ile Asp Arg Arg Thr Val Glu Leu Arg Leu Gly Gly Asn Phe Ile
 50 55 60

Ile His Ile Ser Arg Gln Asp Phe Ala Asn Met Thr Gly Leu Val Asp
 65 70 75 80

Leu Thr Leu Ser Arg Asn Thr Ile Ser His Ile Gln Pro Phe Ser Phe
 85 90 95

Leu Asp Leu Glu Ser Leu Arg Ser Leu His Leu Asp Ser Asn Arg Leu
 100 105 110

Pro Ser Leu Gly Glu Asp Thr Leu Arg Gly Leu Val Asn Leu Gln His
 115 120 125

Leu Ile Val Asn Asn Asn Gln Leu Gly Gly Ile Ala Asp Glu Ala Phe
 130 135 140

Glu Asp Phe Leu Leu Thr Leu Glu Asp Leu Asp Leu Ser Tyr Asn Asn
 145 150 155 160

Leu His Gly Leu Pro Trp Asp Ser Val Arg Arg Met Val Asn Leu His
 165 170 175

Gln Leu Ser Leu Asp His Asn Leu Leu Asp His Ile Ala Glu Gly Thr
 180 185 190

Phe Ala Asp Leu Gln Lys Leu Ala Arg Leu Asp Leu Thr Ser Asn Arg
 195 200 205

Leu Gln Lys Leu Pro Pro Asp Pro Ile Phe Ala Arg Ser Gln Ala Ser
 210 215 220

Ala Leu Thr Ala Thr Pro Phe Ala Pro Pro Leu Ser Phe Ser Phe Gly

225	230	235	240
Gly Asn Pro Leu His Cys Asn Cys Glu Leu Leu Trp Leu Arg Arg Leu	245	250	255
Glu Arg Asp Asp Asp Leu Glu Thr Cys Gly Ser Pro Gly Gly Leu Lys	260	265	270
Gly Arg Tyr Phe Trp His Val Arg Glu Glu Glu Phe Val Cys Glu Pro	275	280	285
Pro Leu Ile Thr Gln His Thr His Lys Leu Leu Val Leu Glu Gly Gln	290	295	300
Ala Ala Thr Leu Lys Cys Lys Ala Ile Gly Asp Pro Ser Pro Leu Ile	305	310	315
His Trp Val Ala Pro Asp Asp Arg Leu Val Gly Asn Ser Ser Arg Thr	325	330	335
Ala Val Tyr Asp Asn Gly Thr Leu Asp Ile Phe Ile Thr Thr Ser Gln	340	345	350
Asp Ser Gly Ala Phe Thr Cys Ile Ala Ala Asn Ala Ala Gly Glu Ala	355	360	365
Thr Ala Met Val Glu Val Ser Ile Val Gln Leu Pro His Leu Ser Asn	370	375	380
Ser Thr Ser Arg Thr Ala Pro Pro Lys Ser Arg Leu Ser Asp Ile Thr	385	390	395
Gly Ser Ser Lys Thr Ser Arg Gly Gly Gly Gly Ser Gly Gly Gly Glu	405	410	415
Pro Pro Lys Ser Pro Pro Glu Arg Ala Val Leu Val Ser Glu Val Thr	420	425	430
Thr Thr Ser Ala Leu Val Lys Trp Ser Val Ser Lys Ser Ala Pro Arg	435	440	445
Val Lys Met Tyr Gln Leu Gln Tyr Asn Cys Ser Asp Asp Glu Val Leu	450	455	460
Ile Tyr Arg Met Ile Pro Ala Ser Asn Lys Ala Phe Val Val Asn Asn	465	470	475
			480

Leu Val Ser Gly Thr Gly Tyr Asp Leu Cys Val Leu Ala Met Trp Asp
 485 490 495

Asp Thr Ala Thr Thr Leu Thr Ala Thr Asn Ile Val Gly Cys Ala Gln
 500 505 510

Phe Phe Thr Lys Ala Asp Tyr Pro Gln Cys Gln Ser Met His Ser Gln
 515 520 525

Ile Leu Gly Gly Thr Met Ile Leu Val Ile Gly Gly Ile Ile Val Ala
 530 535 540

Thr Leu Leu Val Phe Ile Val Ile Leu Met Val Arg Tyr Lys Val Cys
 545 550 555 560

Asn His Glu Ala Pro Ser Lys Met Ala Ala Ala Val Ser Asn Val Tyr
 565 570 575

Ser Gln Thr Asn Gly Ala Gln Pro Pro Pro Pro Ser Ser Ala Pro Ala
 580 585 590

Gly Ala Pro Pro Gln Gly Pro Pro Lys Val Val Val Arg Asn Glu Leu
 595 600 605

Leu Asp Phe Thr Ala Ser Leu Ala Arg Ala Ser Asp Ser Ser Ser Ser
 610 615 620

Ser Ser Leu Gly Ser Gly Glu Ala Ala Gly Leu Gly Arg Ala Pro Trp
 625 630 635 640

Arg Ile Pro Pro Ser Ala Pro Arg Pro Lys Pro Ser Leu Asp Arg Leu
 645 650 655

Met Gly Ala Phe Ala Ser Leu Asp Leu Lys Ser Gln Arg Lys Glu Glu
 660 665 670

Leu Leu Asp Ser Arg Thr Pro Ala Gly Arg Gly Ala Gly Thr Ser Ala
 675 680 685

Arg Gly His His Ser Asp Arg Glu Pro Leu Leu Gly Pro Pro Ala Ala
 690 695 700

Arg Ala Arg Ser Leu Leu Pro Leu Pro Leu Glu Gly Lys Ala Lys Arg
 705 710 715 720

Ser His Ser Phe Asp Met Gly Asp Phe Ala Ala Ala Ala Ala Gly Gly

725 730 735

Val Val Pro Gly Gly Tyr Ser Pro Pro Arg Lys Val Ser Asn Ile Trp
740 745 750

Thr Lys Arg Ser Leu Ser Val Asn Gly Met Leu Leu Pro Phe Glu Glu
755 760 765

Ser Asp Leu Val Gly Ala Arg Gly Thr Phe Gly Ser Ser Glu Trp Val
770 775 780

Met Glu Ser Thr Val
785

<210> 77
<211> 628
<212> PRT
<213> Homo sapiens

<400> 77

Met Ala Ile Leu Pro Leu Leu Leu Cys Leu Leu Pro Leu Ala Pro Ala
1 5 10 15

Ser Ser Pro Pro Gln Ser Ala Thr Pro Ser Pro Cys Pro Arg Arg Cys
20 25 30

Arg Cys Gln Thr Gln Ser Leu Pro Leu Ser Val Leu Cys Pro Gly Ala
35 40 45

Gly Leu Leu Phe Val Pro Pro Ser Leu Asp Arg Arg Ala Ala Glu Leu
50 55 60

Arg Leu Ala Asp Asn Phe Ile Ala Ser Val Arg Arg Arg Asp Leu Ala
65 70 75 80

Asn Met Thr Gly Leu Leu His Leu Ser Leu Ser Arg Asn Thr Ile Arg
85 90 95

His Val Ala Ala Gly Ala Phe Ala Asp Leu Arg Ala Leu Arg Ala Leu
100 105 110

His Leu Asp Gly Asn Arg Leu Thr Ser Leu Gly Glu Gly Gln Leu Arg
115 120 125

Gly Leu Val Asn Leu Arg His Leu Ile Leu Ser Asn Asn Gln Leu Ala
130 135 140

Ala Leu Ala Ala Gly Ala Leu Asp Asp Cys Ala Glu Thr Leu Glu Asp
 145 150 155 160

Leu Asp Leu Ser Tyr Asn Asn Leu Glu Gln Leu Pro Trp Glu Ala Leu
 165 170 175

Gly Arg Leu Gly Asn Val Asn Thr Leu Gly Leu Asp His Asn Leu Leu
 180 185 190

Ala Ser Val Pro Ala Gly Ala Phe Ser Arg Leu His Lys Leu Ala Arg
 195 200 205

Leu Asp Met Thr Ser Asn Arg Leu Thr Thr Ile Pro Pro Asp Pro Leu
 210 215 220

Phe Ser Arg Leu Pro Leu Leu Ala Arg Pro Arg Gly Ser Pro Ala Ser
 225 230 235 240

Ala Leu Val Leu Ala Phe Gly Gly Asn Pro Leu His Cys Asn Cys Glu
 245 250 255

Leu Val Trp Leu Arg Arg Leu Ala Arg Glu Asp Asp Leu Glu Ala Cys
 260 265 270

Ala Ser Pro Pro Ala Leu Gly Gly Arg Tyr Phe Trp Ala Val Gly Glu
 275 280 285

Glu Glu Phe Val Cys Glu Pro Pro Val Val Thr His Arg Ser Pro Pro
 290 295 300

Leu Ala Val Pro Ala Gly Arg Pro Ala Ala Leu Arg Cys Arg Ala Val
 305 310 315 320

Gly Asp Pro Glu Pro Arg Val Arg Trp Val Ser Pro Gln Gly Arg Leu
 325 330 335

Leu Gly Asn Ser Ser Arg Ala Arg Ala Phe Pro Asn Gly Thr Leu Glu
 340 345 350

Leu Leu Val Thr Glu Pro Gly Asp Gly Gly Ile Phe Thr Cys Ile Ala
 355 360 365

Ala Asn Ala Ala Gly Glu Ala Thr Ala Ala Val Glu Leu Thr Val Gly
 370 375 380

Pro Pro Pro Pro Pro Gln Leu Ala Asn Ser Thr Ser Cys Asp Pro Pro
 385 390 395 400

Arg Asp Gly Asp Pro Asp Ala Leu Thr Pro Pro Ser Ala Ala Ser Ala
 405 410 415

Ser Ala Lys Val Ala Asp Thr Gly Pro Pro Thr Asp Arg Gly Val Gln
 420 425 430

Val Thr Glu His Gly Ala Thr Ala Ala Leu Val Gln Trp Pro Asp Gln
 435 440 445

Arg Pro Ile Pro Gly Ile Arg Met Tyr Gln Ile Gln Tyr Asn Ser Ser
 450 455 460

Ala Asp Asp Ile Leu Val Tyr Arg Met Ile Pro Ala Glu Ser Arg Ser
 465 470 475 480

Phe Leu Leu Thr Asp Leu Ala Ser Gly Arg Thr Tyr Asp Leu Cys Val
 485 490 495

Leu Ala Val Tyr Glu Asp Ser Ala Thr Gly Leu Thr Ala Thr Arg Pro
 500 505 510

Val Gly Cys Ala Arg Phe Ser Thr Glu Pro Ala Leu Arg Pro Cys Gly
 515 520 525

Ala Pro His Ala Pro Phe Leu Gly Gly Thr Met Ile Ile Ala Leu Gly
 530 535 540

Gly Val Ile Val Ala Ser Val Leu Val Phe Ile Phe Val Leu Leu Met
 545 550 555 560

Arg Tyr Lys Val His Gly Gly Gln Pro Pro Gly Lys Ala Lys Ile Pro
 565 570 575

Ala Pro Val Ser Ser Val Cys Ser Gln Thr Asn Gly Ala Leu Gly Pro
 580 585 590

Thr Pro Thr Pro Ala Pro Pro Ala Pro Glu Pro Ala Ala Leu Arg Ala
 595 600 605

His Thr Val Val Gln Leu Asp Cys Glu Pro Trp Gly Pro Gly His Glu
 610 615 620

Pro Val Gly Pro
 625

<210> 78
 <211> 673
 <212> PRT
 <213> Homo sapiens

<400> 78

Met Cys Ser Arg Val Pro Leu Leu Leu Pro Leu Leu Leu Leu Ala
 1 5 10 15

Leu Gly Pro Gly Val Gln Gly Cys Pro Ser Gly Cys Gln Cys Ser Gln
 20 25 30

Pro Gln Thr Val Phe Cys Thr Ala Arg Gln Gly Thr Thr Val Pro Arg
 35 40 45

Asp Val Pro Pro Asp Thr Val Gly Leu Tyr Val Phe Glu Asn Gly Ile
 50 55 60

Thr Met Leu Asp Ala Gly Ser Phe Ala Gly Leu Pro Gly Leu Gln Leu
 65 70 75 80

Leu Asp Leu Ser Gln Asn Gln Ile Ala Ser Leu Pro Ser Gly Val Phe
 85 90 95

Gln Pro Leu Ala Asn Leu Ser Asn Leu Asp Leu Thr Ala Asn Arg Leu
 100 105 110

His Glu Ile Thr Asn Glu Thr Phe Arg Gly Leu Arg Arg Leu Glu Arg
 115 120 125

Leu Tyr Leu Gly Lys Asn Arg Ile Arg His Ile Gln Pro Gly Ala Phe
 130 135 140

Asp Thr Leu Asp Arg Leu Leu Glu Leu Lys Leu Gln Asp Asn Glu Leu
 145 150 155 160

Arg Ala Leu Pro Pro Leu Arg Leu Pro Arg Leu Leu Leu Leu Asp Leu
 165 170 175

Ser His Asn Ser Leu Leu Ala Leu Glu Pro Gly Ile Leu Asp Thr Ala
 180 185 190

Asn Val Glu Ala Leu Arg Leu Ala Gly Leu Gly Leu Gln Gln Leu Asp
 195 200 205

Glu Gly Leu Phe Ser Arg Leu Arg Asn Leu His Asp Leu Asp Val Ser
 210 215 220

Asp Asn Gln Leu Glu Arg Val Pro Pro Val Ile Arg Gly Leu Arg Gly
 225 230 235 240

Leu Thr Arg Leu Arg Leu Ala Gly Asn Thr Arg Ile Ala Gln Leu Arg
 245 250 255

Pro Glu Asp Leu Ala Gly Leu Ala Ala Leu Gln Glu Leu Asp Val Ser
 260 265 270

Asn Leu Ser Leu Gln Ala Leu Pro Gly Asp Leu Ser Gly Leu Phe Pro
 275 280 285

Arg Leu Arg Leu Leu Ala Ala Ala Arg Asn Pro Phe Asn Cys Val Cys
 290 295 300

Pro Leu Ser Trp Phe Gly Pro Trp Val Arg Glu Ser His Val Thr Leu
 305 310 315 320

Ala Ser Pro Glu Glu Thr Arg Cys His Phe Pro Pro Lys Asn Ala Gly
 325 330 335

Arg Leu Leu Leu Glu Leu Asp Tyr Ala Asp Phe Gly Cys Pro Ala Thr
 340 345 350

Thr Thr Thr Ala Thr Val Pro Thr Thr Arg Pro Val Val Arg Glu Pro
 355 360 365

Thr Ala Leu Ser Ser Ser Leu Ala Pro Thr Trp Leu Ser Pro Thr Glu
 370 375 380

Pro Ala Thr Glu Ala Pro Ser Pro Pro Ser Thr Ala Pro Pro Thr Val
 385 390 395 400

Gly Pro Val Pro Gln Pro Gln Asp Cys Pro Pro Ser Thr Cys Leu Asn
 405 410 415

Gly Gly Thr Cys His Leu Gly Thr Arg His His Leu Ala Cys Leu Cys
 420 425 430

Pro Glu Gly Phe Thr Gly Leu Tyr Cys Glu Ser Gln Met Gly Gln Gly
 435 440 445

Thr Arg Pro Ser Pro Thr Pro Val Thr Pro Arg Pro Pro Arg Ser Leu
 450 455 460

Thr Leu Gly Ile Glu Pro Val Ser Pro Thr Ser Leu Arg Val Gly Leu

465 470 475 480
 Gln Arg Tyr Leu Gln Gly Ser Ser Val Gln Leu Arg Ser Leu Arg Leu
 485 490 495
 Thr Tyr Arg Asn Leu Ser Gly Pro Asp Lys Arg Leu Val Thr Leu Arg
 500 505 510
 Leu Pro Ala Ser Leu Ala Glu Tyr Thr Val Thr Gln Leu Arg Pro Asn
 515 520 525
 Ala Thr Tyr Ser Val Cys Val Met Pro Leu Gly Pro Gly Arg Val Pro
 530 535 540
 Glu Gly Glu Glu Ala Cys Gly Glu Ala His Thr Pro Pro Ala Val His
 545 550 555 560
 Ser Asn His Ala Pro Val Thr Gln Ala Arg Glu Gly Asn Leu Pro Leu
 565 570 575
 Leu Ile Ala Pro Ala Leu Ala Ala Val Leu Leu Ala Ala Leu Ala Ala
 580 585 590
 Val Gly Ala Ala Tyr Cys Val Arg Arg Gly Arg Ala Met Ala Ala Ala
 595 600 605
 Ala Gln Asp Lys Gly Gln Val Gly Pro Gly Ala Gly Pro Leu Glu Leu
 610 615 620
 Glu Gly Val Lys Val Pro Leu Glu Pro Gly Pro Lys Ala Thr Glu Gly
 625 630 635 640
 Gly Gly Glu Ala Leu Pro Ser Gly Ser Glu Cys Glu Val Pro Leu Met
 645 650 655
 Gly Phe Pro Gly Pro Gly Leu Gln Ser Pro Leu His Ala Lys Pro Tyr
 660 665 670

Ile

<210> 79
 <211> 696
 <212> PRT
 <213> Homo sapiens
 <400> 79

Met Leu Leu Trp Ile Leu Leu Leu Glu Thr Ser Leu Cys Phe Ala Ala
1 5 10 15

Gly Asn Val Thr Gly Asp Val Cys Lys Glu Lys Ile Cys Ser Cys Asn
20 25 30

Glu Ile Glu Gly Asp Leu His Val Asp Cys Glu Lys Lys Gly Phe Thr
35 40 45

Ser Leu Gln Arg Phe Thr Ala Pro Thr Ser Gln Phe Tyr His Leu Phe
50 55 60

Leu His Gly Asn Ser Leu Thr Arg Leu Phe Pro Asn Glu Phe Ala Asn
65 70 75 80

Phe Tyr Asn Ala Val Ser Leu His Met Glu Asn Asn Gly Leu His Glu
85 90 95

Ile Val Pro Gly Ala Phe Leu Gly Leu Gln Leu Val Lys Arg Leu His
100 105 110

Ile Asn Asn Asn Lys Ile Lys Ser Phe Arg Lys Gln Thr Phe Leu Gly
115 120 125

Leu Asp Asp Leu Glu Tyr Leu Gln Ala Asp Phe Asn Leu Leu Arg Asp
130 135 140

Ile Asp Pro Gly Ala Phe Gln Asp Leu Asn Lys Leu Glu Val Leu Ile
145 150 155 160

Leu Asn Asp Asn Leu Ile Ser Thr Leu Pro Ala Asn Val Phe Gln Tyr
165 170 175

Val Pro Ile Thr His Leu Asp Leu Arg Gly Asn Arg Leu Lys Thr Leu
180 185 190

Pro Tyr Glu Glu Val Leu Glu Gln Ile Pro Gly Ile Ala Glu Ile Leu
195 200 205

Leu Glu Asp Asn Pro Trp Asp Cys Thr Cys Asp Leu Leu Ser Leu Lys
210 215 220

Glu Trp Leu Glu Asn Ile Pro Lys Asn Ala Leu Ile Gly Arg Val Val
225 230 235 240

Cys Glu Ala Pro Thr Arg Leu Gln Gly Lys Asp Leu Asn Glu Thr Thr
245 250 255

Glu Gln Asp Leu Cys Pro Leu Lys Asn Arg Val Asp Ser Ser Leu Pro
 260 265 270

Ala Pro Pro Ala Gln Glu Glu Thr Phe Ala Pro Gly Pro Leu Pro Thr
 275 280 285

Pro Phe Lys Thr Asn Gly Gln Glu Asp His Ala Thr Pro Gly Ser Ala
 290 295 300

Pro Asn Gly Gly Thr Lys Ile Pro Gly Asn Trp Gln Ile Lys Ile Arg
 305 310 315 320

Pro Thr Ala Ala Ile Ala Thr Gly Ser Ser Arg Asn Lys Pro Leu Ala
 325 330 335

Asn Ser Leu Pro Cys Pro Gly Gly Cys Ser Cys Asp His Ile Pro Gly
 340 345 350

Ser Gly Leu Lys Met Asn Cys Asn Asn Arg Asn Val Ser Ser Leu Ala
 355 360 365

Asp Leu Lys Pro Lys Leu Ser Asn Val Gln Glu Leu Phe Leu Arg Asp
 370 375 380

Asn Lys Ile His Ser Ile Arg Lys Ser His Phe Val Asp Tyr Lys Asn
 385 390 395 400

Leu Ile Leu Leu Asp Leu Gly Asn Asn Asn Ile Ala Thr Val Glu Asn
 405 410 415

Asn Thr Phe Lys Asn Leu Leu Asp Leu Arg Trp Leu Tyr Met Asp Ser
 420 425 430

Asn Tyr Leu Asp Thr Leu Ser Arg Glu Lys Phe Ala Gly Leu Gln Asn
 435 440 445

Leu Glu Tyr Leu Asn Val Glu Tyr Asn Ala Ile Gln Leu Ile Leu Pro
 450 455 460

Gly Thr Phe Asn Ala Met Pro Lys Leu Arg Ile Leu Ile Leu Asn Asn
 465 470 475 480

Asn Leu Leu Arg Ser Leu Pro Val Asp Val Phe Ala Gly Val Ser Leu
 485 490 495

Ser Lys Leu Ser Leu His Asn Asn Tyr Phe Met Tyr Leu Pro Val Ala
 500 505 510

Gly Val Leu Asp Gln Leu Thr Ser Ile Ile Gln Ile Asp Leu His Gly
 515 520 525

Asn Pro Trp Glu Cys Ser Cys Thr Ile Val Pro Phe Lys Gln Trp Ala
 530 535 540

Glu Arg Leu Gly Ser Glu Val Leu Met Ser Asp Leu Lys Cys Glu Thr
 545 550 555 560

Pro Val Asn Phe Phe Arg Lys Asp Phe Met Leu Leu Ser Asn Asp Glu
 565 570 575

Ile Cys Pro Gln Leu Tyr Ala Arg Ile Ser Pro Thr Leu Thr Ser His
 580 585 590

Ser Lys Asn Ser Thr Gly Leu Ala Glu Thr Gly Thr His Ser Asn Ser
 595 600 605

Tyr Leu Asp Thr Ser Arg Val Ser Ile Ser Val Leu Val Pro Gly Leu
 610 615 620

Leu Leu Val Phe Val Thr Ser Ala Phe Thr Val Val Gly Met Leu Val
 625 630 635 640

Phe Ile Leu Arg Asn Arg Lys Arg Ser Lys Arg Arg Asp Ala Asn Ser
 645 650 655

Ser Ala Ser Glu Ile Asn Ser Leu Gln Thr Val Cys Asp Ser Ser Tyr
 660 665 670

Trp His Asn Gly Pro Tyr Asn Ala Asp Gly Ala His Arg Val Tyr Asp
 675 680 685

Cys Gly Ser His Ser Leu Ser Asp
 690 695

<210> 80
 <211> 834
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (734)..(767)
 <223> Xaa can be any naturally occurring amino acid

<400> 80

Met His Thr Cys Cys Pro Pro Val Thr Leu Glu Gln Asp Leu His Arg
 1 5 10 15

Lys Met His Ser Trp Met Leu Gln Thr Leu Ala Phe Ala Val Thr Ser
 20 25 30

Leu Val Leu Ser Cys Ala Glu Thr Ile Asp Tyr Tyr Gly Glu Ile Cys
 35 40 45

Asp Asn Ala Cys Pro Cys Glu Glu Lys Asp Gly Ile Leu Thr Val Ser
 50 55 60

Cys Glu Asn Arg Gly Ile Ile Ser Leu Ser Glu Ile Ser Pro Pro Arg
 65 70 75 80

Phe Pro Ile Tyr His Leu Leu Leu Ser Gly Asn Leu Leu Asn Arg Leu
 85 90 95

Tyr Pro Asn Glu Phe Val Asn Tyr Thr Gly Ala Ser Ile Leu His Leu
 100 105 110

Gly Ser Asn Val Ile Gln Asp Ile Glu Thr Gly Ala Phe His Gly Leu
 115 120 125

Arg Gly Leu Arg Arg Leu His Leu Asn Asn Asn Lys Leu Glu Leu Leu
 130 135 140

Arg Asp Asp Thr Phe Leu Gly Leu Glu Asn Leu Glu Tyr Leu Gln Val
 145 150 155 160

Asp Tyr Asn Tyr Ile Ser Val Ile Glu Pro Asn Ala Phe Gly Lys Leu
 165 170 175

His Leu Leu Gln Val Leu Ile Leu Asn Asp Asn Leu Leu Ser Ser Leu
 180 185 190

Pro Asn Asn Leu Phe Arg Phe Val Pro Leu Thr His Leu Asp Leu Arg
 195 200 205

Gly Asn Arg Leu Lys Leu Leu Pro Tyr Val Gly Leu Leu Gln His Met
 210 215 220

Asp Lys Val Val Glu Leu Gln Leu Glu Glu Asn Pro Trp Asn Cys Ser
 225 230 235 240

Cys Glu Leu Ile Ser Leu Lys Asp Trp Leu Asp Ser Ile Ser Tyr Ser
 245 250 255
 Ala Leu Val Gly Asp Val Val Cys Glu Thr Pro Phe Arg Leu His Gly
 260 265 270
 Arg Asp Leu Asp Glu Val Ser Lys Gln Glu Leu Cys Pro Arg Arg Leu
 275 280 285
 Ile Ser Asp Tyr Glu Met Arg Pro Gln Thr Pro Leu Ser Thr Thr Gly
 290 295 300
 Tyr Leu His Thr Thr Pro Ala Ser Val Asn Ser Val Ala Thr Ser Ser
 305 310 315 320
 Ser Ala Val Tyr Lys Pro Pro Leu Lys Pro Pro Lys Gly Thr Arg Gln
 325 330 335
 Pro Asn Lys Pro Arg Val Arg Pro Thr Ser Arg Gln Pro Ser Lys Asp
 340 345 350
 Leu Gly Tyr Ser Asn Tyr Gly Pro Ser Ile Ala Tyr Gln Thr Lys Ser
 355 360 365
 Pro Val Pro Leu Glu Cys Pro Thr Ala Cys Ser Cys Asn Leu Gln Ile
 370 375 380
 Ser Asp Leu Gly Leu Asn Val Asn Cys Gln Glu Arg Lys Ile Glu Ser
 385 390 395 400
 Ile Ala Glu Leu Gln Pro Lys Pro Tyr Asn Pro Lys Lys Met Tyr Leu
 405 410 415
 Thr Glu Asn Tyr Ile Ala Val Val Arg Arg Thr Asp Phe Leu Glu Ala
 420 425 430
 Thr Gly Leu Asp Leu Leu His Leu Gly Asn Asn Arg Ile Ser Met Ile
 435 440 445
 Gln Asp Arg Ala Phe Gly Asp Leu Thr Asn Leu Arg Arg Leu Tyr Leu
 450 455 460
 Asn Gly Asn Arg Ile Glu Arg Leu Ser Pro Glu Leu Phe Tyr Gly Leu
 465 470 475 480
 /
 Gln Ser Leu Gln Tyr Leu Phe Leu Gln Tyr Asn Leu Ile Arg Glu Ile

485	490	495
Gln Ser Gly Thr Phe Asp Pro Val Pro Asn Leu Gln Leu Leu Phe Leu		
500	505	510
Asn Asn Asn Leu Leu Gln Ala Met Pro Ser Gly Val Phe Ser Gly Leu		
515	520	525
Thr Leu Leu Arg Leu Asn Leu Arg Ser Asn His Phe Thr Ser Leu Pro		
530	535	540
Val Ser Gly Val Leu Asp Gln Leu Lys Ser Leu Ile Gln Ile Asp Leu		
545	550	555
His Asp Asn Pro Trp Asp Cys Thr Cys Asp Ile Val Gly Met Lys Leu		
565	570	575
Trp Val Glu Gln Leu Lys Val Gly Val Leu Val Asp Glu Val Ile Cys		
580	585	590
Lys Ala Pro Lys Lys Phe Ala Glu Thr Asp Met Arg Ser Ile Lys Ser		
595	600	605
Glu Leu Leu Cys Pro Asp Tyr Ser Asp Val Val Val Ser Thr Pro Thr		
610	615	620
Pro Ser Ser Ile Gln Val Pro Ala Arg Thr Ser Ala Val Thr Pro Ala		
625	630	635
Val Arg Leu Asn Ser Thr Gly Ala Pro Ala Ser Leu Gly Ala Gly Gly		
645	650	655
Gly Ala Ser Ser Val Pro Leu Ser Val Leu Ile Leu Ser Leu Leu Leu		
660	665	670
Val Phe Ile Met Ser Val Phe Val Ala Ala Gly Leu Phe Val Leu Val		
675	680	685
Met Lys Arg Arg Lys Lys Asn Gln Ser Asp His Thr Ser Thr Asn Asn		
690	695	700
Ser Asp Val Ser Ser Phe Asn Met Gln Tyr Ser Val Tyr Gly Gly Gly		
705	710	715
Gly Gly Thr Gly Gly His Pro His Ala His Val His Tyr Xaa Xaa Xaa		
725	730	735

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 740 745 750

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Thr
 755 760 765

Ala Ala Ala Pro Ala Ala Ala Ala Ala Ala Ala Arg Gly Gly Gly Glu
 770 775 780

Ala Gly Lys Pro Pro Leu Ala Glu Pro Arg Leu Gln Arg Gln His His
 785 790 795 800

Arg Ala Pro Gly Gly Pro Ala Val Ala Gly Ala Gly Arg Arg Pro Leu
 805 810 815

Leu Gln Gly His Phe Arg Thr Arg Gln Thr Leu Leu His His Pro Arg
 820 825 830

Arg Gln

<210> 81
 <211> 853
 <212> PRT
 <213> Homo sapiens

<400> 81

Tyr Phe Ser Leu Phe Arg Ser Ile Gln Leu Phe Ala Asp Cys Lys Lys
 1 5 10 15

Met Phe Leu Trp Leu Phe Leu Ile Leu Ser Ala Leu Ile Ser Ser Thr
 20 25 30

Asn Ala Asp Ser Asp Ile Ser Val Glu Ile Cys Asn Val Cys Ser Cys
 35 40 45

Val Ser Val Glu Asn Val Leu Tyr Val Asn Cys Glu Lys Val Ser Val
 50 55 60

Tyr Arg Pro Asn Gln Leu Lys Pro Pro Trp Ser Asn Phe Tyr His Leu
 65 70 75 80

Asn Phe Gln Asn Asn Phe Leu Asn Ile Leu Tyr Pro Asn Thr Phe Leu
 85 90 95

Asn Phe Ser His Ala Val Ser Leu His Leu Gly Asn Asn Lys Leu Gln
 100 105 110

Asn Ile Glu Gly Gly Ala Phe Leu Gly Leu Ser Ala Leu Lys Gln Leu
 115 120 125
 His Leu Asn Asn Asn Glu Leu Lys Ile Leu Arg Ala Asp Thr Phe Leu
 130 135 140
 Gly Ile Glu Asn Leu Glu Tyr Leu Gln Ala Asp Tyr Asn Leu Ile Lys
 145 150 155 160
 Tyr Ile Glu Arg Gly Ala Phe Asn Lys Leu His Lys Leu Lys Val Leu
 165 170 175
 Ile Leu Asn Asp Asn Leu Ile Ser Phe Leu Pro Asp Asn Ile Phe Arg
 180 185 190
 Phe Ala Ser Leu Thr His Leu Asp Ile Arg Gly Asn Arg Ile Gln Lys
 195 200 205
 Leu Pro Tyr Ile Gly Val Leu Glu His Ile Gly Arg Val Val Glu Leu
 210 215 220
 Gln Leu Glu Asp Asn Pro Trp Asn Cys Ser Cys Asp Leu Leu Pro Leu
 225 230 235 240
 Lys Ala Trp Leu Glu Asn Met Pro Tyr Asn Ile Tyr Ile Gly Glu Ala
 245 250 255
 Ile Cys Glu Thr Pro Ser Asp Leu Tyr Gly Arg Leu Leu Lys Glu Thr
 260 265 270
 Asn Lys Gln Glu Leu Cys Pro Met Gly Thr Gly Ser Asp Phe Asp Val
 275 280 285
 Arg Ile Leu Pro Pro Ser Gln Leu Glu Asn Gly Tyr Thr Thr Pro Asn
 290 295 300
 Gly His Thr Thr Gln Thr Ser Leu His Arg Leu Val Thr Lys Pro Pro
 305 310 315 320
 Lys Thr Thr Asn Pro Ser Lys Ile Ser Gly Ile Val Ala Gly Lys Ala
 325 330 335
 Leu Ser Asn Arg Asn Leu Ser Gln Ile Val Ser Tyr Gln Thr Arg Val
 340 345 350

Pro Pro Leu Thr Pro Cys Pro Ala Pro Cys Phe Cys Lys Thr His Pro
 355 360 365

Ser Asp Leu Gly Leu Ser Val Asn Cys Gln Glu Lys Asn Ile Gln Ser
 370 375 380

Met Ser Glu Leu Ile Pro Lys Pro Leu Asn Ala Lys Lys Leu His Val
 385 390 395 400

Asn Gly Asn Ser Ile Lys Asp Val Asp Val Ser Asp Phe Thr Asp Phe
 405 410 415

Glu Gly Leu Asp Leu Leu His Leu Gly Ser Asn Gln Ile Thr Val Ile
 420 425 430

Lys Gly Asp Val Phe His Asn Leu Thr Asn Leu Arg Arg Leu Tyr Leu
 435 440 445

Asn Gly Asn Gln Ile Glu Arg Leu Tyr Pro Glu Ile Phe Ser Gly Leu
 450 455 460

His Asn Leu Gln Tyr Leu Tyr Leu Glu Tyr Asn Leu Ile Lys Glu Ile
 465 470 475 480

Ser Ala Gly Thr Phe Asp Ser Met Pro Asn Leu Gln Leu Leu Tyr Leu
 485 490 495

Asn Asn Asn Leu Leu Lys Ser Leu Pro Val Tyr Ile Phe Ser Gly Ala
 500 505 510

Pro Leu Ala Arg Leu Asn Leu Arg Asn Asn Lys Phe Met Tyr Leu Pro
 515 520 525

Val Ser Gly Val Leu Asp Gln Leu Gln Ser Leu Thr Gln Ile Asp Leu
 530 535 540

Glu Gly Asn Pro Trp Asp Cys Thr Cys Asp Leu Val Ala Leu Lys Leu
 545 550 555 560

Trp Val Glu Lys Leu Ser Asp Gly Ile Val Val Lys Glu Leu Lys Cys
 565 570 575

Glu Thr Pro Val Gln Phe Ala Asn Ile Glu Leu Lys Ser Leu Lys Asn
 580 585 590

Glu Ile Leu Cys Pro Lys Leu Leu Asn Lys Pro Ser Ala Pro Phe Thr
 595 600 605

Ser Pro Ala Pro Ala Ile Thr Phe Thr Thr Pro Leu Gly Pro Ile Arg
 610 615 620

Ser Pro Pro Gly Gly Pro Val Pro Leu Ser Ile Leu Ile Leu Ser Ile
 625 630 635 640

Leu Val Val Leu Ile Leu Thr Val Phe Val Ala Phe Cys Leu Leu Val
 645 650 655

Phe Val Leu Arg Arg Asn Lys Lys Pro Thr Val Lys His Glu Gly Leu
 660 665 670

Gly Asn Pro Asp Cys Gly Ser Met Gln Leu Gln Leu Arg Lys His Asp
 675 680 685

His Lys Thr Asn Lys Lys Asp Gly Leu Ser Thr Glu Ala Phe Ile Pro
 690 695 700

Gln Thr Ile Glu Gln Met Ser Lys Ser His Thr Cys Gly Leu Lys Glu
 705 710 715 720

Ser Glu Thr Gly Phe Met Phe Ser Asp Pro Pro Gly Gln Lys Val Val
 725 730 735

Met Arg Asn Val Ala Asp Lys Glu Lys Asp Leu Leu His Val Asp Thr
 740 745 750

Arg Lys Arg Leu Ser Thr Ile Asp Glu Leu Asp Glu Leu Phe Pro Ser
 755 760 765

Arg Asp Ser Asn Val Phe Ile Gln Asn Phe Leu Glu Ser Lys Lys Glu
 770 775 780

Tyr Asn Ser Ile Gly Val Ser Gly Phe Glu Ile Arg Tyr Pro Glu Lys
 785 790 795 800

Gln Pro Asp Lys Lys Ser Lys Lys Ser Leu Ile Gly Gly Asn His Ser
 805 810 815

Lys Ile Val Val Glu Gln Arg Lys Ser Glu Tyr Phe Glu Leu Lys Ala
 820 825 830

Lys Leu Gln Ser Ser Pro Asp Tyr Leu Gln Val Leu Glu Glu Gln Thr
 835 840 845

Ala Leu Asn Lys Ile
850

<210> 82
<211> 977
<212> PRT
<213> Homo sapiens

<400> 82

Met Lys Pro Ser Ile Ala Glu Met Leu His Arg Gly Arg Met Leu Trp
1 5 10 15

Ile Ile Leu Leu Ser Thr Ile Ala Leu Gly Trp Thr Thr Pro Ile Pro
20 25 30

Leu Ile Glu Asp Ser Glu Glu Ile Asp Glu Pro Cys Phe Asp Pro Cys
35 40 45

Tyr Cys Glu Val Lys Glu Ser Leu Phe His Ile His Cys Asp Ser Lys
50 55 60

Gly Phe Thr Asn Ile Ser Gln Ile Thr Glu Phe Trp Ser Arg Pro Phe
65 70 75 80

Lys Leu Tyr Leu Gln Arg Asn Ser Met Arg Lys Leu Tyr Thr Asn Ser
85 90 95

Phe Leu His Leu Asn Asn Ala Val Ser Ile Asn Leu Gly Asn Asn Ala
100 105 110

Leu Gln Asp Ile Gln Thr Gly Ala Phe Asn Gly Leu Lys Ile Leu Lys
115 120 125

Arg Leu Tyr Leu His Glu Asn Lys Leu Asp Val Phe Arg Asn Asp Thr
130 135 140

Phe Leu Gly Leu Glu Ser Leu Glu Tyr Leu Gln Ala Asp Tyr Asn Val
145 150 155 160

Ile Lys Arg Ile Glu Ser Gly Ala Phe Arg Asn Leu Ser Lys Leu Arg
165 170 175

Val Leu Ile Leu Asn Asp Asn Leu Ile Pro Met Leu Pro Thr Asn Leu
180 185 190

Phe Lys Ala Val Ser Leu Thr His Leu Asp Leu Arg Gly Asn Arg Leu
195 200 205

Lys Val Leu Phe Tyr Arg Gly Met Leu Asp His Ile Gly Arg Ser Leu
 210 215 220
 Met Glu Leu Gln Leu Glu Glu Asn Pro Trp Asn Cys Thr Cys Glu Ile
 225 230 235 240
 Val Gln Leu Lys Ser Trp Leu Glu Arg Ile Pro Tyr Thr Ala Leu Val
 245 250 255
 Gly Asp Ile Thr Cys Glu Thr Pro Phe His Phe His Gly Lys Asp Leu
 260 265 270
 Arg Glu Ile Arg Lys Thr Glu Leu Cys Pro Leu Leu Ser Asp Ser Glu
 275 280 285
 Val Glu Ala Ser Leu Gly Ile Pro His Ser Ser Ser Ser Lys Glu Asn
 290 295 300
 Ala Trp Pro Thr Lys Pro Ser Ser Met Leu Ser Ser Val His Phe Thr
 305 310 315 320
 Ala Ser Ser Val Glu Tyr Lys Ser Ser Asn Lys Gln Pro Lys Pro Thr
 325 330 335
 Lys Gln Pro Arg Thr Pro Arg Pro Pro Ser Thr Ser Gln Ala Leu Tyr
 340 345 350
 Pro Gly Pro Asn Gln Pro Pro Ile Ala Pro Tyr Gln Thr Arg Pro Pro
 355 360 365
 Ile Pro Ile Ile Cys Pro Thr Gly Cys Thr Cys Asn Leu His Ile Asn
 370 375 380
 Asp Leu Gly Leu Thr Val Asn Cys Lys Glu Arg Gly Phe Asn Asn Ile
 385 390 395 400
 Ser Glu Leu Leu Pro Arg Pro Leu Asn Ala Lys Lys Leu Tyr Leu Ser
 405 410 415
 Ser Asn Leu Ile Gln Lys Ile Tyr Arg Ser Asp Phe Trp Asn Phe Ser
 420 425 430
 Ser Leu Asp Leu Leu His Leu Gly Asn Asn Arg Ile Ser Tyr Val Gln
 435 440 445
 Asp Gly Ala Phe Ile Asn Leu Pro Asn Leu Lys Ser Leu Phe Leu Asn

450	455	460
Gly Asn Asp Ile Glu Lys Leu Thr Pro Gly Met Phe Arg Gly Leu Gln		
465	470	475 480
Ser Leu His Tyr Leu Tyr Phe Glu Phe Asn Val Ile Arg Glu Ile Gln		
	485	490 495
Pro Ala Ala Phe Ser Leu Met Pro Asn Leu Lys Leu Leu Phe Leu Asn		
	500	505 510
Asn Asn Leu Leu Arg Thr Leu Pro Thr Asp Ala Phe Ala Gly Thr Ser		
	515	520 525
Leu Ala Arg Leu Asn Leu Arg Lys Asn Tyr Phe Leu Tyr Leu Pro Val		
	530	535 540
Ala Gly Val Leu Glu His Leu Asn Ala Ile Val Gln Ile Asp Leu Asn		
	545	550 555 560
Glu Asn Pro Trp Asp Cys Thr Cys Asp Leu Val Pro Phe Lys Gln Trp		
	565	570 575
Ile Glu Thr Ile Ser Ser Val Ser Val Val Gly Asp Val Leu Cys Arg		
	580	585 590
Ser Pro Glu Asn Leu Thr His Arg Asp Val Arg Thr Ile Glu Leu Glu		
	595	600 605
Val Leu Cys Pro Glu Met Leu His Val Ala Pro Ala Gly Glu Ser Pro		
	610	615 620
Ala Gln Pro Gly Asp Ser His Leu Ile Gly Ala Pro Thr Ser Ala Ser		
	625	630 635 640
Pro Tyr Glu Phe Ser Pro Pro Gly Gly Pro Val Pro Leu Ser Val Leu		
	645	650 655
Ile Leu Ser Leu Leu Val Leu Phe Phe Ser Ala Val Phe Val Ala Ala		
	660	665 670
Gly Leu Phe Ala Tyr Val Leu Arg Arg Arg Arg Lys Lys Leu Pro Phe		
	675	680 685
Arg Ser Lys Arg Gln Glu Gly Val Asp Leu Thr Gly Ile Gln Met Gln		
	690	695 700

Cys His Arg Leu Phe Glu Asp Gly Gly Gly Gly Gly Gly Ser Gly
 705 710 715 720
 Gly Gly Gly Arg Pro Thr Leu Ser Ser Pro Glu Lys Ala Pro Pro Val
 725 730 735
 Gly His Val Tyr Glu Tyr Ile Pro His Pro Val Thr Gln Met Cys Asn
 740 745 750
 Asn Pro Ile Tyr Lys Pro Arg Glu Glu Glu Glu Val Ala Val Ser Ser
 755 760 765
 Ala Gln Glu Ala Gly Ser Ala Glu Arg Gly Gly Pro Gly Thr Gln Pro
 770 775 780
 Pro Gly Met Gly Glu Ala Leu Leu Gly Ser Glu Gln Phe Ala Glu Thr
 785 790 795 800
 Pro Lys Glu Asn His Ser Asn Tyr Arg Thr Leu Leu Glu Lys Glu Lys
 805 810 815
 Glu Trp Ala Leu Ala Val Ser Ser Ser Gln Leu Asn Thr Ile Val Thr
 820 825 830
 Val Asn His His His Pro His His Pro Ala Val Gly Gly Val Ser Gly
 835 840 845
 Val Val Gly Gly Thr Gly Gly Asp Leu Ala Gly Phe Arg His His Glu
 850 855 860
 Lys Asn Gly Gly Val Val Leu Phe Pro Pro Gly Gly Gly Cys Gly Ser
 865 870 875 880
 Gly Ser Met Leu Leu Asp Arg Glu Arg Pro Gln Pro Ala Pro Cys Thr
 885 890 895
 Val Gly Phe Val Asp Cys Leu Tyr Gly Thr Val Pro Lys Leu Lys Glu
 900 905 910
 Leu His Val His Pro Pro Gly Met Gln Tyr Pro Asp Leu Gln Gln Asp
 915 920 925
 Ala Arg Leu Lys Glu Thr Leu Leu Phe Ser Ala Glu Lys Gly Phe Thr
 930 935 940
 Asp His Gln Thr Gln Lys Ser Asp Tyr Leu Glu Leu Arg Ala Lys Leu

945 950 955 960
 Gln Thr Lys Pro Asp Tyr Leu Glu Val Leu Glu Lys Thr Thr Tyr Arg
 965 970 975

 Phe

 <210> 83
 <211> 921
 <212> PRT
 <213> Homo sapiens

 <400> 83

 Met Ala Asp Asp Asp Val Leu Phe Glu Asp Val Tyr Glu Leu Cys Glu
 1 5 10 15

 Val Ile Gly Lys Gly Pro Phe Ser Val Val Arg Arg Cys Ile Asn Arg
 20 25 30

 Glu Thr Gly Gln Gln Phe Ala Val Lys Ile Val Asp Val Ala Lys Phe
 35 40 45

 Thr Ser Ser Pro Gly Leu Ser Thr Glu Asp Leu Lys Arg Glu Ala Ser
 50 55 60

 Ile Cys His Met Leu Lys His Pro His Ile Val Glu Leu Leu Glu Thr
 65 70 75 80

 Tyr Ser Ser Asp Gly Met Leu Tyr Met Val Phe Glu Phe Met Asp Gly
 85 90 95

 Ala Asp Leu Cys Phe Glu Ile Val Lys Arg Ala Asp Ala Gly Phe Val
 100 105 110

 Tyr Ser Glu Ala Val Ala Ser His Tyr Met Arg Gln Ile Leu Glu Ala
 115 120 125

 Leu Arg Tyr Cys His Asp Asn Asn Ile Ile His Arg Asp Val Lys Pro
 130 135 140

 His Cys Val Leu Leu Ala Ser Lys Glu Asn Ser Ala Pro Val Lys Leu
 145 150 155 160

 Gly Gly Phe Gly Val Ala Ile Gln Leu Gly Glu Ser Gly Leu Val Ala
 165 170 175

Gly Gly Arg Val Gly Thr Pro His Phe Met Ala Pro Glu Val Val Lys
 180 185 190

Arg Glu Pro Tyr Gly Lys Pro Val Asp Val Trp Gly Cys Gly Val Ile
 195 200 205

Leu Phe Ile Leu Leu Ser Gly Cys Leu Pro Phe Tyr Gly Thr Lys Glu
 210 215 220

Arg Leu Phe Glu Gly Ile Ile Lys Gly Lys Tyr Lys Met Asn Pro Arg
 225 230 235 240

Gln Trp Ser His Ile Ser Glu Ser Ala Lys Asp Leu Val Arg Arg Met
 245 250 255

Leu Met Leu Asp Pro Ala Glu Arg Ile Thr Val Tyr Glu Ala Leu Asn
 260 265 270

His Pro Trp Leu Lys Glu Arg Asp Arg Tyr Ala Tyr Lys Ile His Leu
 275 280 285

Pro Glu Thr Val Glu Gln Leu Arg Lys Phe Asn Ala Arg Arg Lys Leu
 290 295 300

Lys Gly Ala Val Leu Ala Ala Val Ser Ser His Lys Phe Asn Ser Phe
 305 310 315 320

Tyr Gly Asp Pro Pro Glu Glu Leu Pro Asp Phe Ser Glu Asp Pro Thr
 325 330 335

Ser Ser Gly Leu Leu Ala Ala Glu Arg Ala Val Ser Gln Val Leu Asp
 340 345 350

Ser Leu Glu Glu Ile His Ala Leu Thr Asp Cys Ser Glu Lys Asp Leu
 355 360 365

Asp Phe Leu His Ser Val Phe Gln Asp Gln His Leu His Thr Leu Leu
 370 375 380

Asp Leu Tyr Asp Lys Ile Asn Thr Lys Ser Ser Pro Gln Ile Arg Asn
 385 390 395 400

Pro Pro Ser Asp Ala Val Gln Arg Ala Lys Glu Val Leu Glu Glu Ile
 405 410 415

Ser Cys Tyr Pro Glu Asn Asn Asp Ala Lys Glu Leu Lys Arg Ile Leu
 420 425 430

Thr Gln Pro His Phe Met Ala Leu Leu Gln Thr His Asp Val Val Ala
 435 440 445

His Glu Val Tyr Ser Asp Glu Ala Leu Arg Val Thr Pro Pro Pro Thr
 450 455 460

Ser Pro Tyr Leu Asn Gly Asp Ser Pro Glu Ser Ala Asn Gly Gly Met
 465 470 475 480

Asp Met Glu Asn Val Thr Arg Val Arg Leu Val Gln Phe Gln Lys Asn
 485 490 495

Thr Asp Glu Pro Met Gly Ile Thr Leu Lys Met Asn Glu Leu Asn His
 500 505 510

Cys Ile Val Ala Arg Ile Met His Gly Gly Met Ile His Arg Gln Gly
 515 520 525

Thr Leu His Val Gly Asp Glu Ile Arg Glu Ile Asn Gly Ile Ser Val
 530 535 540

Ala Asn Gln Thr Val Glu Gln Leu Gln Lys Met Leu Arg Glu Met Arg
 545 550 555 560

Gly Ser Ile Thr Phe Lys Ile Val Pro Ser Tyr Arg Thr Gln Ser Ser
 565 570 575

Ser Cys Glu Arg Asp Ser Pro Ser Thr Ser Arg Gln Ser Pro Ala Asn
 580 585 590

Gly His Ser Ser Thr Asn Asn Ser Val Ser Asp Leu Pro Ser Thr Thr
 595 600 605

Gln Pro Lys Gly Arg Gln Ile Tyr Val Arg Ala Gln Phe Glu Tyr Asp
 610 615 620

Pro Ala Lys Asp Asp Leu Ile Pro Cys Lys Glu Ala Gly Ile Arg Phe
 625 630 635 640

Arg Val Gly Asp Ile Ile Gln Ile Ile Ser Lys Asp Asp His Asn Trp
 645 650 655

Trp Gln Gly Lys Leu Glu Asn Ser Lys Asn Gly Thr Ala Gly Leu Ile
 660 665 670

Pro Ser Ser Glu Leu Gln Glu Trp Arg Val Ala Cys Ile Ala Met Glu
675 680 685

Lys Thr Lys Gln Glu Gln Gln Ala Ser Cys Thr Trp Phe Gly Lys Lys
690 695 700

Lys Lys Gln Tyr Lys Asp Lys Tyr Leu Ala Lys His Asn Ala Asp Leu
705 710 715 720

Val Thr Tyr Glu Glu Val Val Lys Leu Pro Ala Phe Lys Arg Lys Thr
725 730 735

Leu Val Leu Leu Gly Ala His Gly Val Gly Arg Arg His Ile Lys Asn
740 745 750

Thr Leu Ile Thr Lys His Pro Asp Arg Phe Ala Tyr Pro Ile Pro His
755 760 765

Thr Thr Arg Pro Pro Lys Arg Asp Glu Glu Asn Gly Lys Asn Tyr Tyr
770 775 780

Phe Val Ser His Asp Gln Met Met Gln Asp Ile Ser Asn Asn Glu Tyr
785 790 795 800

Leu Glu Tyr Gly Ser His Glu Asp Ala Met Tyr Gly Thr Lys Leu Glu
805 810 815

Thr Ile Arg Lys Ile His Glu Gln Gly Leu Ile Ala Ile Leu Asp Val
820 825 830

Glu Pro Gln Ala Leu Lys Val Leu Arg Thr Ala Glu Phe Ala Pro Phe
835 840 845

Val Val Phe Ile Ala Ala Pro Thr Ile Thr Pro Gly Leu Asn Glu Asp
850 855 860

Glu Ser Leu Gln Arg Leu Gln Lys Glu Ser Asp Ile Leu Gln Arg Thr
865 870 875 880

Tyr Ala His Tyr Phe Asp Leu Thr Ile Ile Asn Asn Glu Ile Asp Glu
885 890 895

Thr Ile Arg His Leu Glu Glu Ala Val Glu Leu Val Cys Thr Ala Pro
900 905 910

Gln Trp Val Pro Val Ser Trp Val Tyr
915 920

<210> 84
 <211> 837
 <212> PRT
 <213> Homo sapiens

<400> 84

Met Asn His Leu Glu Gly Ser Ala Glu Val Glu Val Thr Asp Glu Ala
 1 5 10 15

Ala Gly Gly Glu Val Asn Glu Ser Val Glu Ala Asp Leu Glu His Pro
 20 25 30

Glu Val Glu Glu Glu Gln Gln Gln Pro Pro Gln Gln Gln His Tyr Val
 35 40 45

Gly Arg His Gln Arg Gly Arg Ala Leu Glu Asp Leu Arg Ala Gln Leu
 50 55 60

Gly Gln Glu Glu Glu Glu Arg Gly Glu Cys Leu Ala Arg Ser Ala Ser
 65 70 75 80

Thr Glu Ser Gly Phe His Asn His Thr Asp Thr Ala Glu Gly Asp Val
 85 90 95

Ile Ala Ala Ala Arg Asp Gly Tyr Asp Ala Glu Arg Ala Gln Asp Pro
 100 105 110

Glu Asp Glu Ser Ala Tyr Ala Val Gln Tyr Arg Pro Glu Ala Glu Glu
 115 120 125

Tyr Thr Glu Gln Ala Glu Ala Glu His Ala Glu Ala Thr His Arg Arg
 130 135 140

Ala Leu Pro Asn His Leu His Phe His Ser Leu Glu His Glu Glu Ala
 145 150 155 160

Met Asn Ala Ala Tyr Ser Gly Tyr Val Tyr Thr His Arg Leu Phe His
 165 170 175

Arg Gly Glu Asp Glu Pro Tyr Ser Glu Pro Tyr Ala Asp Tyr Gly Gly
 180 185 190

Leu Gln Glu His Val Tyr Glu Glu Ile Gly Asp Ala Pro Glu Leu His
 195 200 205

Ala Arg Asp Gly Leu Arg Leu Tyr Glu Gln Glu Arg Asp Glu Ala Ala

210	215	220
Ala Tyr Arg Gln Glu Ala Leu Gly Ala Arg Leu His His Tyr Asp Glu		
225	230	235 240
Arg Ser Asp Gly Glu Ser Asp Ser Pro Glu Lys Glu Ala Glu Phe Ala		
	245	250 255
Pro Tyr Pro Arg Met Asp Ser Tyr Glu Gln Glu Glu Asp Ile Asp Gln		
	260	265 270
Ile Val Ala Glu Val Lys Gln Ser Met Ser Ser Gln Ser Leu Asp Lys		
	275	280 285
Ala Ala Glu Asp Met Pro Glu Ala Glu Gln Asp Leu Glu Arg Pro Pro		
	290	295 300
Thr Pro Ala Gly Gly Arg Pro Asp Ser Pro Gly Leu Gln Ala Pro Ala		
305	310	315 320
Gly Gln Gln Arg Ala Val Gly Pro Ala Gly Gly Gly Glu Ala Gly Gln		
	325	330 335
Arg Tyr Ser Lys Glu Lys Arg Asp Ala Ile Ser Leu Ala Ile Lys Asp		
	340	345 350
Ile Lys Glu Ala Ile Glu Glu Val Lys Thr Arg Thr Ile Arg Ser Pro		
	355	360 365
Tyr Thr Pro Asp Glu Pro Lys Glu Pro Ile Trp Val Met Arg Gln Asp		
	370	375 380
Ile Ser Pro Thr Arg Asp Cys Asp Asp Gln Arg Pro Met Asp Gly Asp		
385	390	395 400
Ser Pro Ser Pro Gly Ser Ser Ser Pro Leu Gly Ala Glu Ser Ser Ser		
	405	410 415
Thr Ser Leu His Pro Ser Asp Pro Val Glu Val Pro Ile Asn Lys Glu		
	420	425 430
Ser Arg Lys Ser Leu Ala Ser Phe Pro Thr Tyr Val Glu Val Pro Gly		
	435	440 445
Pro Cys Asp Pro Glu Asp Leu Ile Asp Gly Ile Ile Phe Ala Ala Asn		
450	455	460

Tyr Leu Gly Ser Thr Gln Leu Leu Ser Asp Lys Thr Pro Ser Lys Asn
465 470 475 480

Val Arg Met Met Gln Ala Gln Glu Ala Val Ser Arg Ile Lys Met Ala
485 490 495

Gln Lys Leu Ala Lys Ser Arg Lys Lys Ala Pro Glu Gly Glu Ser Gln
500 505 510

Pro Met Thr Glu Val Asp Leu Phe Ile Leu Thr Gln Arg Ile Lys Val
515 520 525

Leu Asn Ala Asp Thr Gln Glu Thr Met Met Asp His Pro Leu Arg Thr
530 535 540

Ile Ser Tyr Ile Ala Asp Ile Gly Asn Ile Val Val Leu Met Ala Arg
545 550 555 560

Arg Arg Ile Pro Arg Ser Asn Ser Gln Glu Asn Val Glu Ala Ser His
565 570 575

Pro Ser Gln Asp Gly Lys Arg Gln Tyr Lys Met Ile Cys His Val Phe
580 585 590

Glu Ser Glu Asp Ala Gln Leu Ile Ala Gln Ser Ile Gly Gln Ala Phe
595 600 605

Ser Val Ala Tyr Gln Glu Phe Leu Arg Ala Asn Gly Ile Asn Pro Glu
610 615 620

Asp Leu Ser Gln Lys Glu Tyr Ser Asp Leu Leu Asn Thr Gln Asp Met
625 630 635 640

Tyr Asn Asp Asp Leu Ile His Phe Ser Lys Ser Glu Asn Cys Lys Asp
645 650 655

Val Phe Ile Glu Lys Gln Lys Gly Glu Ile Leu Gly Val Val Ile Val
660 665 670

Glu Ser Gly Trp Gly Ser Ile Leu Pro Thr Val Ile Ile Ala Asn Met
675 680 685

Met His Gly Gly Pro Ala Glu Lys Ser Gly Lys Leu Asn Ile Gly Asp
690 695 700

Gln Ile Met Ser Ile Asn Gly Thr Ser Leu Val Gly Leu Pro Leu Ser

705 710 715 720
 Thr Cys Gln Ser Ile Ile Lys Gly Leu Glu Asn Gln Ser Arg Val Lys
 725 730 735
 Leu Asn Ile Val Arg Cys Pro Pro Val Thr Thr Val Leu Ile Arg Arg
 740 745 750
 Pro Asp Leu Arg Tyr Gln Leu Gly Phe Ser Val Gln Asn Gly Ile Ile
 755 760 765
 Cys Ser Leu Met Arg Gly Gly Ile Ala Glu Arg Gly Gly Val Arg Val
 770 775 780
 Gly His Arg Ile Ile Glu Ile Asn Gly Gln Ser Val Val Ala Thr Pro
 785 790 795 800
 His Glu Lys Ile Val His Ile Leu Ser Asn Ala Val Gly Glu Ile His
 805 810 815
 Met Lys Thr Met Pro Ala Ala Met Tyr Arg Leu Leu Thr Ala Gln Glu
 820 825 830
 Gln Pro Val Tyr Ile
 835
 <210> 85
 <211> 197
 <212> PRT
 <213> Homo sapiens
 <400> 85
 Met Ala Ala Leu Gly Glu Pro Val Arg Leu Glu Arg Asp Ile Cys Arg
 1 5 10 15
 Ala Ile Glu Leu Leu Glu Lys Leu Gln Arg Ser Gly Glu Val Pro Pro
 20 25 30
 Gln Lys Leu Gln Ala Leu Gln Arg Val Leu Gln Ser Glu Phe Cys Asn
 35 40 45
 Ala Val Arg Glu Val Tyr Glu His Val Tyr Glu Thr Val Asp Ile Ser
 50 55 60
 Ser Ser Pro Glu Val Arg Ala Asn Ala Thr Ala Lys Ala Thr Val Ala
 65 70 75 80

Ala Phe Ala Ala Ser Glu Gly His Ser His Pro Arg Val Val Glu Leu
85 90 95

Pro Lys Thr Glu Glu Gly Leu Gly Phe Asn Ile Met Gly Gly Lys Glu
100 105 110

Gln Asn Ser Pro Ile Tyr Ile Ser Arg Ile Ile Pro Gly Gly Ile Ala
115 120 125

Asp Arg His Gly Gly Leu Lys Arg Gly Asp Gln Leu Leu Ser Val Asn
130 135 140

Gly Val Ser Val Glu Gly Glu His His Glu Lys Ala Val Glu Leu Leu
145 150 155 160

Lys Ala Ala Gln Gly Lys Val Lys Leu Val Val Arg Tyr Thr Pro Lys
165 170 175

Val Leu Glu Glu Met Glu Ser Arg Phe Glu Lys Met Arg Ser Ala Lys
180 185 190

Arg Arg Gln Gln Thr
195

<210> 86
<211> 744
<212> PRT
<213> Homo sapiens

<400> 86

Met Ala Lys Arg Glu Asp Ser Pro Gly Pro Glu Val Gln Pro Met Asp
1 5 10 15

Lys Gln Phe Leu Val Cys Ser Ile Cys Leu Asp Arg Tyr Gln Cys Pro
20 25 30

Lys Val Leu Pro Cys Leu His Thr Phe Cys Glu Arg Cys Leu Gln Asn
35 40 45

Tyr Ile Pro Ala Gln Ser Leu Thr Leu Ser Cys Pro Val Cys Arg Gln
50 55 60

Thr Ser Ile Leu Pro Glu Gln Gly Val Ser Ala Leu Gln Asn Asn Phe
65 70 75 80

Phe Ile Ser Ser Leu Met Glu Ala Met Gln Gln Ala Pro Asp Gly Ala
85 90 95

His Asp Pro Glu Asp Pro His Pro Leu Ser Val Val Ala Gly Arg Pro
 100 105 110

Phe Ser Cys Pro Asn His Glu Gly Lys Thr Met Glu Phe Tyr Cys Glu
 115 120 125

Ala Cys Glu Thr Ala Met Cys Gly Glu Cys Arg Ala Gly Glu His Arg
 130 135 140

Glu His Gly Thr Val Leu Leu Arg Asp Val Val Glu Gln His Lys Ala
 145 150 155 160

Ala Leu Gln Arg Gln Leu Glu Ala Val Arg Gly Arg Leu Pro Gln Leu
 165 170 175

Ser Ala Ala Ile Ala Leu Val Gly Gly Ile Ser Gln Gln Leu Gln Glu
 180 185 190

Arg Lys Ala Glu Ala Leu Ala Gln Ile Ser Ala Ala Phe Glu Asp Leu
 195 200 205

Glu Gln Ala Leu Gln Gln Arg Lys Gln Ala Leu Val Ser Asp Leu Glu
 210 215 220

Thr Ile Cys Gly Ala Lys Gln Lys Val Leu Gln Thr Gln Leu Asp Thr
 225 230 235 240

Leu Arg Gln Gly Gln Glu His Ile Gly Ser Ser Cys Ser Phe Ala Glu
 245 250 255

Gln Ala Leu Arg Leu Gly Ser Ala Pro Glu Val Leu Leu Val Arg Lys
 260 265 270

His Met Arg Glu Arg Leu Ala Ala Leu Ala Ala Gln Ala Phe Pro Glu
 275 280 285

Arg Pro His Glu Asn Ala Gln Leu Glu Leu Val Leu Glu Val Asp Gly
 290 295 300

Leu Arg Arg Ser Val Leu Asn Leu Gly Ala Leu Leu Thr Thr Ser Ala
 305 310 315 320

Thr Ala His Glu Thr Val Ala Thr Gly Glu Gly Leu Arg Gln Ala Leu
 325 330 335

Val Gly Gln Pro Ala Ser Leu Thr Val Thr Ala Lys Asp Lys Asp Gly

340	345	350
Arg Leu Val Arg Thr Gly Ser Ala Glu Leu Arg Ala Glu Ile Thr Gly		
355	360	365
Pro Asp Gly Thr Arg Leu Pro Val Pro Val Val Asp His Lys Asn Gly		
370	375	380
Thr Tyr Glu Leu Val Tyr Thr Ala Arg Thr Glu Gly Glu Leu Leu Leu		
385	390	395
Ser Val Leu Leu Tyr Gly Gln Pro Val Arg Gly Ser Pro Phe Arg Val		
405	410	415
Arg Ala Leu Arg Pro Gly Asp Leu Pro Pro Ser Pro Asp Asp Val Lys		
420	425	430
Arg Arg Val Lys Ser Pro Gly Gly Pro Gly Ser His Val Arg Gln Lys		
435	440	445
Ala Val Arg Arg Pro Ser Ser Met Tyr Ser Thr Gly Gly Lys Arg Lys		
450	455	460
Asp Asn Pro Ile Glu Asp Glu Leu Val Phe Arg Val Gly Ser Arg Gly		
465	470	475
Arg Glu Lys Gly Glu Phe Thr Asn Leu Gln Gly Val Ser Ala Ala Ser		
485	490	495
Ser Gly Arg Ile Val Val Ala Asp Ser Asn Asn Gln Cys Ile Gln Val		
500	505	510
Phe Ser Asn Glu Gly Gln Phe Lys Phe Arg Phe Gly Val Arg Gly Arg		
515	520	525
Ser Pro Gly Gln Leu Gln Arg Pro Thr Gly Val Ala Val Asp Thr Asn		
530	535	540
Gly Asp Ile Ile Val Ala Asp Tyr Asp Asn Arg Trp Val Ser Ile Phe		
545	550	555
Ser Pro Glu Gly Lys Phe Lys Thr Lys Ile Gly Ala Gly Arg Leu Met		
565	570	575
Gly Pro Lys Gly Val Ala Val Asp Arg Asn Gly His Ile Ile Val Val		
580	585	590

Asp Asn Lys Ser Cys Cys Val Phe Thr Phe Gln Pro Asn Gly Lys Leu
 595 600 605

Val Gly Arg Phe Gly Gly Arg Gly Ala Thr Asp Arg His Phe Ala Gly
 610 615 620

Pro His Phe Val Ala Val Ser Asn Lys Asn Glu Val Val Val Thr Asp
 625 630 635 640

Phe His Asn His Ser Glu Lys Val Tyr Ser Ala Asp Gly Glu Phe Leu
 645 650 655

Phe Lys Phe Gly Ser His Gly Glu Gly Asn Gly Gln Phe Asn Ala Pro
 660 665 670

Thr Gly Val Ala Val Asp Ser Asn Gly Asn Ile Ile Val Ala Asp Trp
 675 680 685

Gly Asn Ser Arg Ile Gln Val Phe Asp Ser Ser Gly Ser Phe Leu Ser
 690 695 700

Tyr Ile Asn Thr Ser Ala Glu Pro Leu Tyr Gly Pro Gln Gly Leu Ala
 705 710 715 720

Leu Thr Ser Asp Gly His Val Val Val Ala Asp Ala Gly Asn His Cys
 725 730 735

Phe Lys Ala Tyr Arg Tyr Leu Gln
 740

<210> 87
 <211> 618
 <212> PRT
 <213> Homo sapiens

<400> 87

Met Thr Gln Glu Tyr Asp Asn Lys Arg Pro Val Leu Ala Leu Gln Asn
 1 5 10 15

Glu Ala Leu Tyr Pro Gln Arg Arg Ser Tyr Thr Ser Glu Asp Glu Ala
 20 25 30

Trp Lys Ser Phe Leu Glu Asn Pro Leu Thr Ala Ala Thr Lys Ala Met
 35 40 45

Met Ser Ile Asn Gly Asp Glu Asp Ser Ala Ala Ala Leu Gly Leu Leu
 50 55 60

Tyr Asp Tyr Tyr Lys Val Pro Arg Glu Arg Arg Ser Ser Thr Ala Lys
 65 70 75 80

Pro Glu Val Glu His Pro Glu Pro Asp His Ser Lys Arg Asn Ser Ile
 85 90 95

Pro Ile Val Thr Glu Gln Pro Leu Ile Ser Ala Gly Glu Asn Arg Val
 100 105 110

Gln Val Leu Lys Asn Val Pro Phe Asn Ile Val Leu Pro His Gly Asn
 115 120 125

Gln Leu Gly Ile Asp Lys Arg Gly His Leu Thr Ala Pro Asp Thr Thr
 130 135 140

Val Thr Val Ser Ile Ala Thr Met Pro Thr His Ser Ile Lys Thr Glu
 145 150 155 160

Thr Gln Pro His Gly Phe Ala Val Gly Ile Pro Pro Ala Val Tyr His
 165 170 175

Pro Glu Pro Thr Glu Arg Val Val Val Phe Asp Arg Asn Leu Asn Thr
 180 185 190

Asp Gln Phe Ser Ser Gly Ala Gln Ala Pro Asn Ala Gln Arg Arg Thr
 195 200 205

Pro Asp Ser Thr Phe Ser Glu Thr Phe Lys Glu Gly Val Gln Glu Val
 210 215 220

Phe Phe Pro Ser Asp Leu Ser Leu Arg Met Pro Gly Met Asn Ser Glu
 225 230 235 240

Asp Tyr Val Phe Asp Ser Val Ser Gly Asn Asn Phe Glu Tyr Thr Leu
 245 250 255

Glu Ala Ser Lys Ser Leu Arg Gln Lys Pro Gly Asp Ser Thr Met Thr
 260 265 270

Tyr Leu Asn Lys Gly Gln Phe Tyr Pro Ile Thr Leu Lys Glu Val Ser
 275 280 285

Ser Ser Glu Gly Ile His His Pro Ile Ser Lys Val Arg Ser Val Ile
 290 295 300

Met Val Val Phe Ala Glu Asp Lys Ser Arg Glu Asp Gln Leu Arg His
 305 310 315 320

Trp Lys Tyr Trp His Ser Arg Gln His Thr Ala Lys Gln Arg Cys Ile
 325 330 335

Asp Ile Ala Asp Tyr Lys Glu Ser Phe Asn Thr Ile Ser Asn Ile Glu
 340 345 350

Glu Ile Ala Tyr Asn Ala Ile Ser Phe Thr Trp Asp Ile Asn Asp Glu
 355 360 365

Ala Lys Val Phe Ile Ser Val Asn Cys Leu Ser Thr Asp Phe Ser Ser
 370 375 380

Gln Lys Gly Val Lys Gly Leu Pro Leu Asn Ile Gln Val Asp Thr Tyr
 385 390 395 400

Ser Tyr Asn Asn Arg Ser Asn Lys Pro Val His Arg Ala Tyr Cys Gln
 405 410 415

Ile Lys Val Phe Cys Asp Lys Gly Ala Glu Arg Lys Ile Arg Asp Glu
 420 425 430

Glu Arg Lys Gln Ser Lys Arg Lys Val Ser Asp Val Lys Val Pro Leu
 435 440 445

Leu Pro Ser His Lys Arg Met Asp Ile Thr Val Phe Lys Pro Phe Ile
 450 455 460

Asp Leu Asp Thr Gln Pro Val Leu Phe Ile Pro Asp Val His Phe Ala
 465 470 475 480

Asn Leu Gln Arg Gly Thr His Val Leu Pro Ile Ala Ser Glu Glu Leu
 485 490 495

Glu Gly Glu Gly Ser Val Leu Lys Arg Gly Pro Tyr Gly Thr Glu Asp
 500 505 510

Asp Phe Ala Val Pro Pro Ser Thr Lys Leu Ala Arg Ile Glu Glu Pro
 515 520 525

Lys Arg Val Leu Leu Tyr Val Arg Lys Glu Ser Glu Glu Val Phe Asp
 530 535 540

Ala Leu Met Leu Lys Thr Pro Ser Leu Lys Gly Leu Met Glu Ala Ile
 545 550 555 560

Ser Asp Lys Tyr Asp Val Pro His Asp Lys Ile Gly Lys Ile Phe Lys
565 570 575

Lys Cys Lys Lys Gly Ile Leu Val Asn Met Asp Asp Asn Ile Val Lys
580 585 590

His Tyr Ser Asn Glu Asp Thr Phe Gln Leu Gln Ile Glu Glu Ala Gly
595 600 605

Gly Ser Tyr Lys Leu Thr Leu Thr Glu Ile
610 615

<210> 88
<211> 531
<212> PRT
<213> Homo sapiens

<400> 88

Met Asp Gly Ile Val Thr Glu Val Ala Val Gly Val Lys Arg Gly Ser
1 5 10 15

Asp Glu Leu Leu Ser Gly Ser Val Leu Ser Ser Pro Asn Ser Asn Met
20 25 30

Ser Ser Met Val Val Thr Ala Asn Gly Asn Asp Ser Lys Lys Phe Lys
35 40 45

Gly Glu Asp Lys Met Asp Gly Ala Pro Ser Arg Val Leu His Ile Arg
50 55 60

Lys Leu Pro Gly Glu Val Thr Glu Thr Glu Val Ile Ala Leu Gly Leu
65 70 75 80

Pro Phe Gly Lys Val Thr Asn Ile Leu Met Leu Lys Gly Lys Asn Gln
85 90 95

Ala Phe Leu Glu Leu Ala Thr Glu Glu Ala Ala Ile Thr Met Val Asn
100 105 110

Tyr Tyr Ser Ala Val Thr Pro His Leu Arg Asn Gln Pro Ile Tyr Ile
115 120 125

Gln Tyr Ser Asn His Lys Glu Leu Lys Thr Asp Asn Thr Leu Asn Gln
130 135 140

Arg Ala Gln Ala Val Leu Gln Ala Val Thr Ala Val Gln Thr Ala Asn

145	150	155	160
Thr Pro Leu Ser Gly Thr Thr Val Ser Glu Ser Ala Val Thr Pro Ala	165	170	175
Gln Ser Pro Val Leu Arg Ile Ile Ile Asp Asn Met Tyr Tyr Pro Val	180	185	190
Thr Leu Asp Val Leu His Gln Ile Phe Ser Lys Phe Gly Ala Val Leu	195	200	205
Lys Ile Ile Thr Phe Thr Lys Asn Asn Gln Phe Gln Ala Leu Leu Gln	210	215	220
Tyr Gly Asp Pro Val Asn Ala Gln Gln Ala Lys Leu Ala Leu Asp Gly	225	230	235
Gln Asn Ile Tyr Asn Ala Cys Cys Thr Leu Arg Ile Asp Phe Ser Lys	245	250	255
Leu Val Asn Leu Asn Val Lys Tyr Asn Asn Asp Lys Ser Arg Asp Tyr	260	265	270
Thr Arg Pro Asp Leu Pro Ser Gly Asp Gly Gln Pro Ala Leu Asp Pro	275	280	285
Ala Ile Ala Ala Ala Phe Ala Lys Glu Thr Ser Leu Leu Ala Val Pro	290	295	300
Gly Ala Leu Ser Pro Leu Ala Ile Pro Asn Ala Ala Ala Ala Ala Ala	305	310	315
Ala Ala Ala Ala Gly Arg Val Gly Met Pro Gly Val Ser Ala Gly Gly	325	330	335
Asn Thr Val Leu Leu Val Ser Asn Leu Asn Glu Glu Met Val Thr Pro	340	345	350
Gln Ser Leu Phe Thr Leu Phe Gly Val Tyr Gly Asp Val Gln Arg Val	355	360	365
Lys Ile Leu Tyr Asn Lys Lys Asp Ser Ala Leu Ile Gln Met Ala Asp	370	375	380
Gly Asn Gln Ser Gln Leu Ala Met Asn His Leu Asn Gly Gln Lys Met	385	390	395
			400

Tyr Gly Lys Ile Ile Arg Val Thr Leu Ser Lys His Gln Thr Val Gln
 405 410 415

Leu Pro Arg Glu Gly Leu Asp Asp Gln Gly Leu Thr Lys Asp Phe Gly
 420 425 430

Asn Ser Pro Leu His Arg Phe Lys Lys Pro Gly Ser Lys Asn Phe Gln
 435 440 445

Asn Ile Phe Pro Pro Ser Ala Thr Leu His Leu Ser Asn Ile Pro Pro
 450 455 460

Ser Val Ala Glu Glu Asp Leu Arg Thr Leu Phe Ala Asn Thr Gly Gly
 465 470 475 480

Thr Val Lys Ala Phe Lys Phe Phe Gln Asp His Lys Met Ala Leu Leu
 485 490 495

Gln Met Ala Thr Val Glu Glu Ala Ile Gln Ala Leu Ile Asp Leu His
 500 505 510

Asn Tyr Asn Leu Gly Glu Asn His His Leu Arg Val Ser Phe Ser Lys
 515 520 525

Ser Thr Ile
 530

<210> 89
 <211> 521
 <212> PRT
 <213> Homo sapiens

<400> 89

Met Asn Ser Ser Thr Pro Ser Thr Ala Asn Gly Asn Asp Ser Lys Lys
 1 5 10 15

Phe Lys Arg Asp Arg Pro Pro Cys Ser Pro Ser Arg Val Leu His Leu
 20 25 30

Arg Lys Ile Pro Cys Asp Val Thr Glu Ala Glu Ile Ile Ser Leu Gly
 35 40 45

Leu Pro Phe Gly Lys Val Thr Asn Leu Leu Met Leu Lys Gly Lys Ser
 50 55 60

Gln Ala Phe Leu Glu Met Ala Ser Glu Glu Ala Ala Val Thr Met Val
 65 70 75 80

Asn Tyr Tyr Thr Pro Ile Thr Pro His Leu Arg Ser Gln Pro Val Tyr
 85 90 95

Ile Gln Tyr Ser Asn His Arg Glu Leu Lys Thr Asp Asn Leu Pro Asn
 100 105 110

Gln Ala Arg Ala Gln Ala Ala Leu Gln Ala Val Ser Ala Val Gln Ser
 115 120 125

Gly Ser Leu Ala Leu Ser Gly Gly Pro Ser Asn Glu Gly Thr Val Leu
 130 135 140

Pro Gly Gln Ser Pro Val Leu Arg Ile Ile Ile Glu Asn Leu Phe Tyr
 145 150 155 160

Pro Val Thr Leu Glu Val Leu His Gln Ile Phe Ser Lys Phe Gly Thr
 165 170 175

Val Leu Lys Ile Ile Thr Phe Thr Lys Asn Asn Gln Phe Gln Ala Leu
 180 185 190

Leu Gln Tyr Ala Asp Pro Val Asn Ala His Tyr Ala Lys Met Ala Leu
 195 200 205

Asp Gly Gln Asn Ile Tyr Asn Ala Cys Cys Thr Leu Arg Ile Asp Phe
 210 215 220

Ser Lys Leu Thr Ser Leu Asn Val Lys Tyr Asn Asn Asp Lys Ser Arg
 225 230 235 240

Asp Phe Thr Arg Leu Asp Leu Pro Thr Gly Asp Gly Gln Pro Ser Leu
 245 250 255

Glu Pro Pro Met Ala Ala Ala Phe Gly Ala Pro Gly Ile Ile Ser Ser
 260 265 270

Pro Tyr Ala Gly Ala Ala Gly Phe Ala Pro Ala Ile Gly Phe Pro Gln
 275 280 285

Ala Thr Gly Leu Ser Val Pro Ala Val Pro Gly Ala Leu Gly Pro Leu
 290 295 300

Thr Ile Thr Ser Ser Ala Val Thr Gly Arg Met Ala Ile Pro Gly Ala
 305 310 315 320

Ser Gly Ile Pro Gly Asn Ser Val Leu Leu Val Thr Asn Leu Asn Pro
325 330 335

Asp Leu Ile Thr Pro His Gly Leu Phe Ile Leu Phe Gly Val Tyr Gly
340 345 350

Asp Val His Arg Val Lys Ile Met Phe Asn Lys Lys Glu Asn Ala Leu
355 360 365

Val	Gln	Met	Ala	Asp	Ala	Asn	Gln	Ala	Gln	Leu	Ala	Met	Asn	His	Leu
370						375					380				

Ser Gly Gln Arg Leu Tyr Gly Lys Val Leu Arg Ala Thr Leu Ser Lys
385 390 395 400

His Gln Ala Val Gln Leu Pro Arg Glu Gly Gln Glu Asp Gln Gly Leu
405 410 415

Thr Lys Asp Phe Ser Asn Ser Pro Leu His Arg Phe Lys Lys Pro Gly
420 425 430

Ser Lys Asn Phe Gln Asn Ile Phe Pro Pro Ser Ala Thr Leu His Leu
435 440 445

Ser Asn Ile Pro Pro Ser Val Thr Val Asp Asp Leu Lys Asn Leu Phe
450 455 460

Ile Glu Ala Gly Cys Ser Val Lys Ala Phe Lys Phe Phe Gln Lys Asp
465 470 475 480

Arg Lys Met Ala Leu Ile Gln Leu Gly Ser Val Glu Glu Ala Ile Gln
485 490 495

Ala Leu Ile Glu Leu His Asn His Asp Leu Gly Glu Asn His His Leu
500 505 510

Arg Val Ser Phe Ser Lys Ser Thr Ile
515 520

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<210> 90
<211> 557
<212> PRT
<213> Homo sapiens
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<400> 90

Met Asp Gly Ile Val Pro Asp Ile Ala Val Gly Thr Lys Arg Gly Ser
1 5 10 15

Asp Glu Leu Phe Ser Thr Cys Val Thr Asn Gly Pro Phe Ile Met Ser
 20 25 30

Ser Asn Ser Ala Ser Ala Ala Asn Gly Asn Asp Ser Lys Lys Phe Lys
 35 40 45

Gly Asp Ser Arg Ser Ala Gly Val Pro Ser Arg Val Ile His Ile Arg
 50 55 60

Lys Leu Pro Ile Asp Val Thr Glu Gly Glu Val Ile Ser Leu Gly Leu
 65 70 75 80

Pro Phe Gly Lys Val Thr Asn Leu Leu Met Leu Lys Gly Lys Asn Gln
 85 90 95

Ala Phe Ile Glu Met Asn Thr Glu Glu Ala Ala Asn Thr Met Val Asn
 100 105 110

Tyr Tyr Thr Ser Val Thr Pro Val Leu Arg Gly Gln Pro Ile Tyr Ile
 115 120 125

Gln Phe Ser Asn His Lys Glu Leu Lys Thr Asp Ser Ser Pro Asn Gln
 130 135 140

Ala Arg Ala Gln Ala Ala Leu Gln Ala Val Asn Ser Val Gln Ser Gly
 145 150 155 160

Asn Leu Ala Leu Ala Ala Ser Ala Ala Ala Val Asp Ala Gly Met Ala
 165 170 175

Met Ala Gly Gln Ser Pro Val Leu Arg Ile Ile Val Glu Asn Leu Phe
 180 185 190

Tyr Pro Val Thr Leu Asp Val Leu His Gln Ile Phe Ser Lys Phe Gly
 195 200 205

Thr Val Leu Lys Ile Ile Thr Phe Thr Lys Asn Asn Gln Phe Gln Ala
 210 215 220

Leu Leu Gln Tyr Ala Asp Pro Val Ser Ala Gln His Ala Lys Leu Ser
 225 230 235 240

Leu Asp Gly Gln Asn Ile Tyr Asn Ala Cys Cys Thr Leu Arg Ile Asp
 245 250 255

Phe Ser Lys Leu Thr Ser Leu Asn Val Lys Tyr Asn Asn Asp Lys Ser

260	265	270
Arg Asp Tyr Thr Arg Pro Asp Leu Pro Ser Gly Asp Ser Gln Pro Ser		
275	280	285
Leu Asp Gln Thr Met Ala Ala Ala Phe Gly Ala Pro Gly Ile Ile Ser		
290	295	300
Ala Ser Pro Tyr Ala Gly Ala Gly Phe Pro Pro Thr Phe Ala Ile Pro		
305	310	315
Gln Ala Ala Gly Leu Ser Val Pro Asn Val His Gly Ala Leu Ala Pro		
325	330	335
Leu Ala Ile Pro Ser Ala Ala Ala Ala Ala Ala Ala Gly Arg Ile		
340	345	350
Ala Ile Pro Gly Leu Ala Gly Ala Gly Asn Ser Val Leu Leu Val Ser		
355	360	365
Asn Leu Asn Pro Glu Arg Val Thr Pro Gln Ser Leu Phe Ile Leu Phe		
370	375	380
Gly Val Tyr Gly Asp Val Gln Arg Val Lys Ile Leu Phe Asn Lys Lys		
385	390	395
Glu Asn Ala Leu Val Gln Met Ala Asp Gly Asn Gln Ala Gln Leu Ala		
405	410	415
Met Ser His Leu Asn Gly His Lys Leu His Gly Lys Pro Ile Arg Ile		
420	425	430
Thr Leu Ser Lys His Gln Asn Val Gln Leu Pro Arg Glu Gly Gln Glu		
435	440	445
Asp Gln Gly Leu Thr Lys Asp Tyr Gly Asn Ser Pro Leu His Arg Phe		
450	455	460
Lys Lys Pro Gly Ser Lys Asn Phe Gln Asn Ile Phe Pro Pro Ser Ala		
465	470	475
Thr Leu His Leu Ser Asn Ile Pro Pro Ser Val Ser Glu Glu Asp Leu		
485	490	495
Lys Val Leu Phe Ser Ser Asn Gly Gly Val Val Lys Gly Phe Lys Phe		
500	505	510

Phe Gln Lys Asp Arg Lys Met Ala Leu Ile Gln Met Gly Ser Val Glu
 515 520 525

Glu Ala Val Gln Ala Leu Ile Asp Leu His Asn His Asp Leu Gly Glu
 530 535 540

Asn His His Leu Arg Val Ser Phe Ser Lys Ser Thr Ile
 545 550 555

<210> 91
 <211> 534
 <212> PRT
 <213> Homo sapiens

<400> 91

Met Ile Trp Tyr Ile Leu Ile Ile Gly Ile Leu Leu Pro Gln Ser Leu
 1 5 10 15

Ala His Pro Gly Phe Phe Thr Ser Ile Gly Gln Met Thr Asp Leu Ile
 20 25 30

His Thr Glu Lys Asp Leu Val Thr Ser Leu Lys Asp Tyr Ile Lys Ala
 35 40 45

Glu Glu Asp Lys Leu Glu Gln Ile Lys Lys Trp Ala Glu Lys Leu Asp
 50 55 60

Arg Leu Thr Ser Thr Ala Thr Lys Asp Pro Glu Gly Phe Val Gly His
 65 70 75 80

Pro Val Asn Ala Phe Lys Leu Met Lys Arg Leu Asn Thr Glu Trp Ser
 85 90 95

Glu Leu Glu Asn Leu Val Leu Lys Asp Met Ser Asp Gly Phe Ile Ser
 100 105 110

Asn Leu Thr Ile Gln Arg Pro Val Leu Ser Asn Asp Glu Asp Gln Val
 115 120 125

Gly Ala Ala Lys Ala Leu Leu Arg Leu Gln Asp Thr Tyr Asn Leu Asp
 130 135 140

Thr Asp Thr Ile Ser Lys Gly Asn Leu Pro Gly Val Lys His Lys Ser
 145 150 155 160

Phe Leu Thr Ala Glu Asp Cys Phe Glu Leu Gly Lys Val Ala Tyr Thr
 165 170 175

Glu Ala Asp Tyr Tyr His Thr Glu Leu Trp Met Glu Gln Ala Leu Arg
 180 185 190

Gln Leu Asp Glu Gly Glu Ile Ser Thr Ile Asp Lys Val Ser Val Leu
 195 200 205

Asp Tyr Leu Ser Tyr Ala Val Tyr Gln Gln Gly Asp Leu Asp Lys Ala
 210 215 220

Leu Leu Leu Thr Lys Lys Leu Leu Glu Leu Asp Pro Glu His Gln Arg
 225 230 235 240

Ala Asn Gly Asn Leu Lys Tyr Phe Glu Tyr Ile Met Ala Lys Glu Lys
 245 250 255

Asp Val Asn Lys Ser Ala Ser Asp Asp Gln Ser Asp Gln Lys Thr Thr
 260 265 270

Pro Lys Lys Lys Gly Val Ala Val Asp Tyr Leu Pro Glu Arg Gln Lys
 275 280 285

Tyr Glu Met Leu Cys Arg Gly Glu Gly Ile Lys Met Thr Pro Arg Arg
 290 295 300

Gln Lys Lys Leu Phe Cys Arg Tyr His Asp Gly Asn Arg Asn Pro Lys
 305 310 315 320

Phe Ile Leu Ala Pro Ala Lys Gln Glu Asp Glu Trp Asp Lys Pro Arg
 325 330 335

Ile Ile Arg Phe His Asp Ile Ile Ser Asp Ala Glu Ile Glu Ile Val
 340 345 350

Lys Asp Leu Ala Lys Pro Arg Leu Ser Arg Ala Thr Val His Asp Pro
 355 360 365

Glu Thr Gly Lys Leu Thr Thr Ala Gln Tyr Arg Val Ser Lys Ser Ala
 370 375 380

Trp Leu Ser Gly Tyr Glu Asn Pro Val Val Ser Arg Ile Asn Met Arg
 385 390 395 400

Ile Gln Asp Leu Thr Gly Leu Asp Val Ser Thr Ala Glu Glu Leu Gln
 405 410 415

Val Ala Asn Tyr Gly Val Gly Gly Gln Tyr Glu Pro His Phe Asp Phe
 420 425 430

Ala Arg Lys Asp Glu Pro Asp Ala Phe Lys Glu Leu Gly Thr Gly Asn
 435 440 445

Arg Ile Ala Thr Trp Leu Phe Tyr Met Ser Asp Val Ser Ala Gly Gly
 450 455 460

Ala Thr Val Phe Pro Glu Val Gly Ala Ser Val Trp Pro Lys Lys Gly
 465 470 475 480

Thr Ala Val Phe Trp Tyr Asn Leu Phe Ala Ser Gly Glu Gly Asp Tyr
 485 490 495

Ser Thr Arg His Ala Ala Cys Pro Val Leu Val Gly Asn Lys Trp Val
 500 505 510

Ser Asn Lys Trp Leu His Glu Arg Gly Gln Glu Phe Arg Arg Pro Cys
 515 520 525

Thr Leu Ser Glu Leu Glu
 530

<210> 92
 <211> 535
 <212> PRT
 <213> Homo sapiens

<400> 92

Met Lys Leu Trp Val Ser Ala Leu Leu Met Ala Trp Phe Gly Val Leu
 1 5 10 15

Ser Cys Val Gln Ala Glu Phe Phe Thr Ser Ile Gly His Met Thr Asp
 20 25 30

Leu Ile Tyr Ala Glu Lys Glu Leu Val Gln Ser Leu Lys Glu Tyr Ile
 35 40 45

Leu Val Glu Glu Ala Lys Leu Ser Lys Ile Lys Ser Trp Ala Asn Lys
 50 55 60

Met Glu Ala Leu Thr Ser Lys Ser Ala Ala Asp Ala Glu Gly Tyr Leu
 65 70 75 80

Ala His Pro Val Asn Ala Tyr Lys Leu Val Lys Arg Leu Asn Thr Asp
 85 90 95

Trp Pro Ala Leu Glu Asp Leu Val Leu Gln Asp Ser Ala Ala Gly Phe
 100 105 110

Ile Ala Asn Leu Ser Val Gln Arg Gln Phe Phe Pro Thr Asp Glu Asp
 115 120 125

Glu Ile Gly Ala Ala Lys Ala Leu Met Arg Leu Gln Asp Thr Tyr Arg
 130 135 140

Leu Asp Pro Gly Thr Ile Ser Arg Gly Glu Leu Pro Gly Thr Lys Tyr
 145 150 155 160

Gln Ala Met Leu Ser Val Asp Asp Cys Phe Gly Met Gly Arg Ser Ala
 165 170 175

Tyr Asn Glu Gly Asp Tyr Tyr His Thr Val Leu Trp Met Glu Gln Val
 180 185 190

Leu Lys Gln Leu Asp Ala Gly Glu Glu Ala Thr Thr Thr Lys Ser Gln
 195 200 205

Val Leu Asp Tyr Leu Ser Tyr Ala Val Phe Gln Leu Gly Asp Leu His
 210 215 220

Arg Ala Leu Glu Leu Thr Arg Arg Leu Leu Ser Leu Asp Pro Ser His
 225 230 235 240

Glu Arg Ala Gly Gly Asn Leu Arg Tyr Phe Glu Gln Leu Leu Glu Glu
 245 250 255

Glu Arg Glu Lys Thr Leu Thr Asn Gln Thr Glu Ala Glu Leu Ala Thr
 260 265 270

Pro Glu Gly Ile Tyr Glu Arg Pro Val Asp Tyr Leu Pro Glu Arg Asp
 275 280 285

Val Tyr Glu Ser Leu Cys Arg Gly Glu Gly Val Lys Leu Thr Pro Arg
 290 295 300

Arg Gln Lys Arg Leu Phe Cys Arg Tyr His His Gly Asn Arg Ala Pro
 305 310 315 320

Gln Leu Leu Ile Ala Pro Phe Lys Glu Glu Asp Glu Trp Asp Ser Pro
 325 330 335

His Ile Val Arg Tyr Tyr Asp Val Met Ser Asp Glu Glu Ile Glu Arg

340 345 350
 Ile Lys Glu Ile Ala Lys Pro Lys Leu Ala Arg Ala Thr Val Arg Asp
 355 360 365
 Pro Lys Thr Gly Val Leu Thr Val Ala Ser Tyr Arg Val Ser Lys Ser
 370 375 380
 Ser Trp Leu Glu Glu Asp Asp Asp Pro Val Val Ala Arg Val Asn Arg
 385 390 395 400
 Arg Met Gln His Ile Thr Gly Leu Thr Val Lys Thr Ala Glu Leu Leu
 405 410 415
 Gln Val Ala Asn Tyr Gly Val Gly Gly Gln Tyr Glu Pro His Phe Asp
 420 425 430
 Phe Ser Arg Asn Asp Glu Arg Asp Thr Phe Lys His Leu Gly Thr Gly
 435 440 445
 Asn Arg Val Ala Thr Phe Leu Asn Tyr Met Ser Asp Val Glu Ala Gly
 450 455 460
 Gly Ala Thr Val Phe Pro Asp Leu Gly Ala Ala Ile Trp Pro Lys Lys
 465 470 475 480
 Gly Thr Ala Val Phe Trp Tyr Asn Leu Leu Arg Ser Gly Glu Gly Asp
 485 490 495
 Tyr Arg Thr Arg His Ala Ala Cys Pro Val Leu Val Gly Cys Lys Trp
 500 505 510
 Val Ser Asn Lys Trp Phe His Glu Arg Gly Gln Glu Phe Leu Arg Pro
 515 520 525
 Cys Gly Ser Thr Glu Val Asp
 530 535
 <210> 93
 <211> 755
 <212> PRT
 <213> Homo sapiens
 <400> 93
 Met Glu Ala Val Ile Glu Lys Glu Cys Ser Ala Leu Gly Gly Leu Phe
 1 5 10 15

Gln Thr Ile Ile Ser Asp Met Lys Gly Ser Tyr Pro Val Trp Glu Asp
20 25 30

Phe Ile Asn Lys Ala Gly Lys Leu Gln Ser Gln Leu Arg Thr Thr Val
35 40 45

Val Ala Ala Ala Ala Phe Leu Asp Ala Phe Gln Lys Val Ala Asp Met
50 55 60

Ala Thr Asn Thr Arg Gly Gly Thr Arg Glu Ile Gly Ser Ala Leu Thr
65 70 75 80

Arg Met Cys Met Arg His Arg Ser Ile Glu Ala Lys Leu Arg Gln Phe
85 90 95

Ser Ser Ala Leu Ile Asp Cys Leu Ile Asn Pro Leu Gln Glu Gln Met
100 105 110

Glu Glu Trp Lys Lys Val Ala Asn Gln Leu Asp Lys Asp His Ala Lys
115 120 125

Glu Tyr Lys Lys Ala Arg Gln Glu Ile Lys Lys Lys Ser Ser Asp Thr
130 135 140

Leu Lys Leu Gln Lys Lys Ala Lys Lys Gly Arg Gly Asp Ile Gln Pro
145 150 155 160

Gln Leu Asp Ser Ala Leu Gln Asp Val Asn Asp Lys Tyr Leu Leu Leu
165 170 175

Glu Glu Thr Glu Lys Gln Ala Val Arg Lys Ala Leu Ile Glu Glu Arg
180 185 190

Gly Arg Phe Cys Thr Phe Ile Ser Met Leu Arg Pro Val Ile Glu Glu
195 200 205

Glu Ile Ser Met Leu Gly Glu Ile Thr His Leu Gln Thr Ile Ser Glu
210 215 220

Asp Leu Lys Ser Leu Thr Met Asp Pro His Lys Leu Pro Ser Ser Ser
225 230 235 240

Glu Gln Val Ile Leu Asp Leu Lys Gly Ser Asp Tyr Ser Trp Ser Tyr
245 250 255

Gln Thr Pro Pro Ser Ser Pro Ser Thr Thr Met Ser Arg Lys Ser Ser
260 265 270

Val Cys Ser Ser Leu Asn Ser Val Asn Ser Ser Asp Ser Arg Ser Ser
 275 280 285

Gly Ser His Ser His Ser Pro Ser Ser His Tyr Arg Tyr Arg Ser Ser
 290 295 300

Asn Leu Ala Gln Gln Ala Pro Val Arg Leu Ser Ser Val Ser Ser His
 305 310 315 320

Asp Ser Gly Phe Ile Ser Gln Asp Ala Phe Gln Ser Lys Ser Pro Ser
 325 330 335

Pro Met Pro Pro Glu Ala Pro Asn Gln Leu Ser Asn Gly Phe Ser His
 340 345 350

Tyr Ser Leu Ser Ser Glu Ser His Val Gly Pro Thr Gly Ala Gly Leu
 355 360 365

Phe Pro His Cys Leu Pro Ala Ser Arg Leu Leu Pro Arg Val Thr Ser
 370 375 380

Val His Leu Pro Asp Tyr Ala His Tyr Tyr Thr Ile Gly Pro Gly Met
 385 390 395 400

Phe Pro Ser Ser Gln Ile Pro Ser Trp Lys Asp Trp Ala Lys Pro Gly
 405 410 415

Pro Tyr Asp Gln Pro Leu Val Asn Thr Leu Gln Arg Arg Lys Glu Lys
 420 425 430

Arg Glu Pro Asp Pro Asn Gly Gly Gly Pro Thr Thr Ala Ser Gly Pro
 435 440 445

Pro Ala Ala Ala Glu Glu Ala Gln Arg Pro Arg Ser Met Thr Val Ser
 450 455 460

Ala Ala Thr Arg Pro Gly Glu Glu Met Glu Ala Cys Glu Glu Leu Ala
 465 470 475 480

Leu Ala Leu Ser Arg Gly Leu Gln Leu Asp Thr Gln Arg Ser Ser Arg
 485 490 495

Asp Ser Leu Gln Cys Ser Ser Gly Tyr Ser Thr Gln Thr Thr Thr Pro
 500 505 510

Cys Cys Ser Glu Asp Thr Ile Pro Ser Gln Val Ser Asp Tyr Asp Tyr
 515 520 525

Phe Ser Val Ser Gly Asp Gln Glu Ala Asp Gln Gln Glu Phe Asp Lys
 530 535 540

Ser Ser Thr Ile Pro Arg Asn Ser Asp Ile Ser Gln Ser Tyr Arg Arg
 545 550 555 560

Met Phe Gln Ala Lys Arg Pro Ala Ser Thr Ala Gly Leu Pro Thr Thr
 565 570 575

Leu Gly Pro Ala Met Val Thr Pro Gly Val Ala Thr Ile Arg Arg Thr
 580 585 590

Pro Ser Thr Lys Pro Ser Val Arg Arg Gly Thr Ile Gly Ala Gly Pro
 595 600 605

Ile Pro Ile Lys Thr Pro Val Ile Pro Val Lys Thr Pro Thr Val Pro
 610 615 620

Asp Leu Pro Gly Val Met Pro Ala Pro Pro Asp Gly Pro Glu Glu Arg
 625 630 635 640

Gly Glu His Ser Pro Glu Ser Pro Ser Val Gly Glu Gly Pro Gln Gly
 645 650 655

Val Thr Ser Met Pro Ser Ser Met Trp Ser Gly Gln Ala Ser Val Asn
 660 665 670

Pro Pro Leu Pro Gly Pro Lys Pro Ser Ile Pro Glu Glu His Arg Gln
 675 680 685

Ala Ile Pro Glu Ser Glu Ala Glu Asp Gln Glu Arg Glu Pro Pro Ser
 690 695 700

Ala Thr Val Ser Pro Gly Gln Ile Pro Glu Ser Asp Pro Ala Asp Leu
 705 710 715 720

Ser Pro Arg Asp Thr Pro Gln Gly Glu Asp Met Leu Asn Ala Ile Arg
 725 730 735

Arg Gly Val Lys Leu Lys Lys Thr Thr Thr Asn Asp Arg Ser Ala Pro
 740 745 750

Arg Phe Ser
 755

<210> 94
 <211> 211
 <212> PRT
 <213> Homo sapiens

<400> 94

Met Cys Met Arg His Arg Ser Ile Glu Thr Lys Leu Arg Gln Phe Thr
 1 5 10 15

Asn Ala Leu Leu Glu Ser Leu Ile Asn Pro Leu Gln Glu Arg Ile Glu
 20 25 30

Asp Trp Lys Lys Ala Ala Asn Gln Leu Asp Lys Asp His Ala Lys Glu
 35 40 45

Tyr Lys Arg Ala Arg His Glu Ile Lys Lys Lys Ser Ser Asp Thr Leu
 50 55 60

Lys Leu Gln Lys Lys Ala Arg Lys Gly Lys Gly Asp Leu Gln Pro Gln
 65 70 75 80

Leu Asp Ser Ala Leu Gln Asp Val Asn Asp Met Tyr Leu Leu Leu Glu
 85 90 95

Glu Thr Glu Lys Gln Ala Val Arg Arg Ala Leu Ile Glu Glu Arg Gly
 100 105 110

Arg Phe Cys Thr Phe Ile Thr Phe Leu Gln Pro Val Val Asn Gly Glu
 115 120 125

Leu Thr Met Leu Gly Glu Ile Thr His Leu Gln Gly Ile Ile Asp Asp
 130 135 140

Leu Val Val Leu Thr Ala Glu Pro His Lys Leu Pro Pro Ala Ser Glu
 145 150 155 160

Gln Val Ile Lys Asp Leu Lys Gly Ser Asp Tyr Ser Trp Ser Tyr Gln
 165 170 175

Thr Pro Pro Ser Val Pro Ser Glu Pro Phe Val Ser Phe Leu Ser Val
 180 185 190

Arg Phe Trp Lys Asn Ser Pro Leu Leu Pro Ala Pro Ser Thr Pro Ser
 195 200 205

Ser Pro Ile

210

<210> 95
 <211> 117
 <212> PRT
 <213> Homo sapiens

<400> 95

Met Arg Leu Arg Gln Ala Pro Glu Ser Arg Lys Val Phe Ile Gln Arg
 1 5 10 15

Asp Tyr Ser Ser Gly Thr Gly Cys Gln Phe Gln Thr Met Phe Ser Met
 20 25 30

Glu Leu Glu Asn Gln Ile Asp Arg Gln Gln Phe Glu Glu Ile Val Gln
 35 40 45

Thr Leu Asn Asn Leu Tyr Ala Glu Ala Glu Lys Leu Gly Gly Gln Ser
 50 55 60

Tyr Leu Glu Gly Cys Leu Ala Cys Leu Thr Ala Tyr Thr Ile Phe Leu
 65 70 75 80

Cys Leu Glu Thr His Tyr Gln Lys Leu Leu Lys Lys Val Ser Lys Cys
 85 90 95

Ile Gln Glu Gln Asn Glu Lys Ile Tyr Val Pro Gln Gly Leu Leu Leu
 100 105 110

Thr Asp Ser Ile Glu
 115

<210> 96
 <211> 104
 <212> PRT
 <213> Homo sapiens

<400> 96

Met Glu Asn Arg Ile Asp Arg Gln Gln Phe Glu Glu Thr Val Arg Thr
 1 5 10 15

Leu Asn Asn Leu Tyr Ala Glu Ala Glu Lys Leu Gly Gly Gln Ser Tyr
 20 25 30

Leu Glu Gly Cys Leu Ala Cys Leu Thr Ala Tyr Thr Ile Phe Leu Cys
 35 40 45

Met Glu Thr His Tyr Glu Lys Val Leu Lys Lys Val Ser Lys Tyr Ile

50 55 60
 Gln Glu Gln Asn Glu Lys Ile Tyr Ala Pro Gln Gly Leu Leu Leu Thr
 65 70 75 80
 Asp Pro Ile Glu Arg Gly Leu Arg Val Ile Glu Ile Thr Ile Tyr Glu
 85 90 95
 Asp Arg Gly Met Ser Ser Gly Arg
 100
 <210> 97
 <211> 890
 <212> PRT
 <213> Homo sapiens
 <400> 97
 Met Asp Ser Asn Thr Ala Pro Leu Gly Pro Ser Cys Pro Gln Pro Pro
 1 5 10 15
 Pro Ala Pro Gln Pro Gln Ala Arg Ser Arg Leu Asn Ala Thr Ala Ser
 20 25 30
 Leu Glu Gln Glu Arg Ser Glu Arg Pro Arg Ala Pro Gly Pro Gln Ala
 35 40 45
 Gly Pro Gly Pro Gly Val Arg Asp Ala Ala Ala Pro Ala Glu Pro Gln
 50 55 60
 Ala Gln His Thr Arg Ser Arg Glu Arg Ala Asp Gly Thr Gly Pro Thr
 65 70 75 80
 Lys Gly Asp Met Glu Ile Pro Phe Glu Glu Val Leu Glu Arg Ala Lys
 85 90 95
 Ala Gly Asp Pro Lys Ala Gln Thr Glu Val Gly Lys His Tyr Leu Gln
 100 105 110
 Leu Ala Gly Asp Thr Asp Glu Glu Leu Asn Ser Cys Thr Ala Val Asp
 115 120 125
 Trp Leu Val Leu Ala Ala Lys Gln Gly Arg Arg Glu Ala Val Lys Leu
 130 135 140
 Leu Arg Arg Cys Leu Ala Asp Arg Arg Gly Ile Thr Ser Glu Asn Glu
 145 150 155 160

Arg Glu Val Arg Gln Leu Ser Ser Glu Thr Asp Leu Glu Arg Ala Val
 165 170 175

Arg Lys Ala Ala Leu Val Met Tyr Trp Lys Leu Asn Pro Lys Lys Lys
 180 185 190

Lys Gln Val Ala Val Ala Glu Leu Leu Glu Asn Val Gly Gln Val Asn
 195 200 205

Glu His Asp Gly Gly Ala Gln Pro Gly Pro Val Pro Lys Ser Leu Gln
 210 215 220

Lys Gln Arg Arg Met Leu Glu Arg Leu Val Ser Ser Glu Ser Lys Asn
 225 230 235 240

Tyr Ile Ala Leu Asp Asp Phe Val Glu Ile Thr Lys Lys Tyr Ala Lys
 245 250 255

Gly Val Ile Pro Ser Ser Leu Phe Leu Gln Asp Asp Glu Asp Asp Asp
 260 265 270

Glu Leu Ala Gly Lys Ser Pro Glu Asp Leu Pro Leu Arg Leu Lys Val
 275 280 285

Val Lys Tyr Pro Leu His Ala Ile Met Glu Ile Lys Glu Tyr Leu Ile
 290 295 300

Asp Met Ala Ser Arg Ala Gly Met His Trp Leu Ser Thr Ile Ile Pro
 305 310 315 320

Thr His His Ile Asn Ala Leu Ile Phe Phe Phe Ile Ile Ser Asn Leu
 325 330 335

Thr Ile Asp Phe Phe Ala Phe Phe Ile Pro Leu Val Ile Phe Tyr Leu
 340 345 350

Ser Phe Ile Ser Met Val Ile Cys Thr Leu Lys Val Phe Gln Asp Ser
 355 360 365

Lys Ala Trp Glu Asn Phe Arg Thr Leu Thr Asp Leu Leu Leu Arg Phe
 370 375 380

Glu Pro Asn Leu Asp Val Glu Gln Ala Glu Val Asn Phe Gly Trp Asn
 385 390 395 400

His Leu Glu Pro Tyr Ala His Phe Leu Leu Ser Val Phe Phe Val Ile
 405 410 415

Phe Ser Phe Pro Ile Ala Ser Lys Asp Cys Ile Pro Cys Ser Glu Leu
 420 425 430

Ala Val Ile Thr Gly Phe Phe Thr Val Thr Ser Tyr Leu Ser Leu Ser
 435 440 445

Thr His Ala Glu Pro Tyr Thr Arg Arg Ala Leu Ala Thr Glu Val Thr
 450 455 460

Ala Gly Leu Leu Ser Leu Leu Pro Ser Met Pro Leu Asn Trp Pro Tyr
 465 470 475 480

Leu Lys Val Leu Gly Gln Thr Phe Ile Thr Val Pro Val Gly His Leu
 485 490 495

Val Val Leu Asn Val Ser Val Pro Cys Leu Leu Tyr Val Tyr Leu Leu
 500 505 510

Tyr Leu Phe Phe Arg Met Ala Gln Leu Arg Asn Phe Lys Gly Thr Tyr
 515 520 525

Cys Tyr Leu Val Pro Tyr Leu Val Cys Phe Met Trp Cys Glu Leu Ser
 530 535 540

Val Val Ile Leu Leu Glu Ser Thr Gly Leu Gly Leu Leu Arg Ala Ser
 545 550 555 560

Ile Gly Tyr Phe Leu Phe Leu Phe Ala Leu Pro Ile Leu Val Ala Gly
 565 570 575

Leu Ala Leu Val Gly Val Leu Gln Phe Ala Arg Trp Phe Thr Ser Leu
 580 585 590

Glu Leu Thr Lys Ile Ala Val Thr Val Ala Val Cys Ser Val Pro Leu
 595 600 605

Leu Leu Arg Trp Trp Thr Lys Ala Ser Phe Ser Val Val Gly Met Val
 610 615 620

Lys Ser Leu Thr Arg Ser Ser Met Val Lys Leu Ile Leu Val Trp Leu
 625 630 635 640

Thr Ala Ile Val Leu Phe Cys Trp Phe Tyr Val Tyr Arg Ser Glu Gly
 645 650 655

Met Lys Val Tyr Asn Ser Thr Leu Thr Trp Gln Gln Tyr Gly Ala Leu
660 665 670

Cys Gly Pro Arg Ala Trp Lys Glu Thr Asn Met Ala Arg Thr Gln Ile
675 680 685

Leu Cys Ser His Leu Glu Gly His Arg Val Thr Trp Thr Gly Arg Phe
690 695 700

Lys Tyr Val Arg Val Thr Asp Ile Asp Asn Ser Ala Glu Ser Ala Ile
705 710 715 720

Asn Met Leu Pro Phe Phe Ile Gly Asp Trp Met Arg Cys Leu Tyr Gly
725 730 735

Glu Ala Tyr Pro Ala Cys Ser Pro Gly Asn Thr Ser Thr Ala Glu Glu
740 745 750

Glu Leu Cys Arg Leu Lys Leu Leu Ala Lys His Pro Cys His Ile Lys
755 760 765

Lys Phe Asp Arg Tyr Lys Phe Glu Ile Thr Val Gly Met Pro Phe Ser
770 775 780

Ser Gly Ala Asp Gly Ser Arg Ser Arg Glu Glu Asp Asp Val Thr Lys
785 790 795 800

Asp Ile Val Leu Arg Ala Ser Ser Glu Phe Lys Ser Val Leu Leu Ser
805 810 815

Leu Arg Gln Gly Ser Leu Ile Glu Phe Ser Thr Ile Leu Glu Gly Arg
820 825 830

Leu Gly Ser Lys Trp Pro Val Phe Glu Leu Lys Ala Ile Ser Cys Leu
835 840 845

Asn Cys Met Ala Gln Leu Ser Pro Thr Arg Arg His Val Lys Ile Glu
850 855 860

His Asp Trp Arg Ser Thr Val His Gly Ala Val Lys Phe Ala Phe Asp
865 870 875 880

Phe Phe Phe Phe Pro Phe Leu Ser Ala Ala
885 890

<210> 98

<211> 528

<212> PRT

<213> Homo sapiens

<400> 98

Met Ala Glu His Leu Glu Leu Leu Ala Glu Met Pro Met Val Gly Arg
 1 5 10 15

Met Ser Thr Gln Glu Arg Leu Lys His Ala Gln Lys Arg Arg Ala Gln
 20 25 30

Gln Val Lys Met Trp Ala Gln Ala Glu Lys Glu Ala Gln Gly Lys Lys
 35 40 45

Gly Pro Gly Glu Arg Pro Arg Lys Glu Ala Ala Ser Gln Gly Leu Leu
 50 55 60

Lys Gln Val Leu Phe Pro Pro Ser Val Val Leu Leu Glu Ala Ala Ala
 65 70 75 80

Arg Asn Asp Leu Glu Glu Val Arg Gln Phe Leu Gly Ser Gly Val Ser
 85 90 95

Pro Asp Leu Ala Asn Glu Asp Gly Leu Thr Ala Leu His Gln Cys Cys
 100 105 110

Ile Asp Asp Phe Arg Glu Met Val Gln Gln Leu Leu Glu Ala Gly Ala
 115 120 125

Asn Ile Asn Ala Cys Asp Ser Glu Cys Trp Thr Pro Leu His Ala Ala
 130 135 140

Ala Thr Cys Gly His Leu His Leu Val Glu Leu Leu Ile Ala Ser Gly
 145 150 155 160

Ala Asn Leu Leu Ala Val Asn Thr Asp Gly Asn Met Pro Tyr Asp Leu
 165 170 175

Cys Asp Asp Glu Gln Thr Leu Asp Cys Leu Glu Thr Ala Met Ala Asp
 180 185 190

Arg Gly Ile Thr Gln Asp Ser Ile Glu Ala Ala Arg Ala Val Pro Glu
 195 200 205

Leu Arg Met Leu Asp Asp Ile Arg Ser Arg Leu Gln Ala Gly Ala Asp
 210 215 220

Leu His Ala Pro Leu Asp His Gly Ala Thr Leu Leu His Val Ala Ala

225	230	235	240
Ala Asn Gly Phe Ser Glu Ala Ala Ala Leu Leu Leu Glu His Arg Ala	245	250	255
Ser Leu Ser Ala Lys Asp Gln Asp Gly Trp Glu Pro Leu His Ala Ala	260	265	270
Ala Tyr Trp Gly Gln Val Pro Leu Val Glu Leu Leu Val Ala His Gly	275	280	285
Ala Asp Leu Asn Ala Lys Ser Leu Met Asp Glu Thr Pro Leu Asp Val	290	295	300
Cys Gly Asp Glu Glu Val Arg Ala Lys Leu Leu Glu Leu Lys His Lys	305	310	315
His Asp Ala Leu Leu Arg Ala Gln Ser Arg Gln Arg Ser Leu Leu Arg	325	330	335
Arg Arg Thr Ser Ser Ala Gly Ser Arg Gly Lys Val Val Arg Arg Val	340	345	350
Ser Leu Thr Gln Arg Thr Asp Leu Tyr Arg Lys Gln His Ala Gln Glu	355	360	365
Ala Ile Val Trp Gln Gln Pro Pro Pro Thr Ser Pro Glu Pro Pro Glu	370	375	380
Asp Asn Asp Asp Arg Gln Thr Gly Ala Glu Leu Arg Pro Pro Pro Pro	385	390	395
Glu Glu Asp Asn Pro Glu Val Val Arg Pro His Asn Gly Arg Val Gly	405	410	415
Gly Ser Pro Val Arg His Leu Tyr Ser Lys Arg Leu Asp Arg Ser Val	420	425	430
Ser Tyr Gln Leu Ser Pro Leu Asp Ser Thr Thr Pro His Thr Leu Val	435	440	445
His Asp Lys Ala His His Thr Leu Ala Asp Leu Lys Arg Gln Arg Ala	450	455	460
Ala Ala Lys Leu Gln Arg Pro Pro Pro Glu Gly Pro Glu Ser Pro Glu	465	470	475
			480

Thr Ala Glu Pro Gly Leu Pro Gly Asp Thr Val Thr Pro Gln Pro Asp
 485 490 495

Cys Gly Phe Arg Ala Gly Gly Asp Pro Pro Leu Leu Lys Leu Thr Ala
 500 505 510

Pro Ala Val Glu Ala Pro Val Glu Arg Arg Pro Cys Cys Leu Leu Met
 515 520 525

<210> 99

<211> 567

<212> PRT

<213> Homo sapiens

<400> 99

Met Ala Ser His Val Asp Leu Leu Thr Glu Leu Gln Leu Leu Glu Lys
 1 5 10 15

Val Pro Thr Leu Glu Arg Leu Arg Ala Ala Gln Lys Arg Arg Ala Gln
 20 25 30

Gln Leu Lys Lys Trp Ala Gln Tyr Glu Gln Asp Leu Gln His Arg Lys
 35 40 45

Arg Lys His Glu Arg Lys Arg Ser Thr Gly Gly Arg Arg Lys Lys Val
 50 55 60

Ser Phe Glu Ala Ser Val Ala Leu Leu Glu Ala Ser Leu Arg Asn Asp
 65 70 75 80

Ala Glu Glu Val Arg Tyr Phe Leu Lys Asn Lys Val Ser Pro Asp Leu
 85 90 95

Cys Asn Glu Asp Gly Leu Thr Ala Leu His Gln Cys Cys Ile Asp Asn
 100 105 110

Phe Glu Glu Ile Val Lys Leu Leu Leu Ser His Gly Ala Asn Val Asn
 115 120 125

Ala Lys Asp Asn Glu Leu Trp Thr Pro Leu His Ala Ala Ala Thr Cys
 130 135 140

Gly His Ile Asn Leu Val Lys Ile Leu Val Gln Tyr Gly Ala Asp Leu
 145 150 155 160

Leu Ala Val Asn Ser Asp Gly Asn Met Pro Tyr Asp Leu Cys Glu Asp
 165 170 175

Glu Pro Thr Leu Asp Val Ile Glu Thr Cys Met Ala Tyr Gln Gly Ile
 180 185 190
 Thr Gln Glu Lys Ile Asn Glu Met Arg Val Ala Pro Glu Gln Gln Met
 195 200 205
 Ile Ala Asp Ile His Cys Met Ile Ala Ala Gly Gln Asp Leu Asp Trp
 210 215 220
 Ile Asp Ala Gln Gly Ala Thr Leu Leu His Ile Ala Gly Ala Asn Gly
 225 230 235 240
 Tyr Leu Arg Ala Ala Glu Leu Leu Leu Asp His Gly Val Arg Val Asp
 245 250 255
 Val Lys Asp Trp Asp Gly Trp Glu Pro Leu His Ala Ala Ala Phe Trp
 260 265 270
 Gly Gln Met Gln Met Ala Glu Leu Leu Val Ser His Gly Ala Ser Leu
 275 280 285
 Ser Ala Arg Thr Ser Met Asp Glu Met Pro Ile Asp Leu Cys Glu Glu
 290 295 300
 Glu Glu Phe Lys Val Leu Leu Leu Glu Leu Lys His Lys His Asp Val
 305 310 315 320
 Ile Met Lys Ser Gln Leu Arg His Lys Ser Ser Leu Ser Arg Arg Thr
 325 330 335
 Ser Ser Ala Gly Ser Arg Gly Lys Val Val Arg Arg Ala Ser Leu Ser
 340 345 350
 Asp Arg Thr Asn Leu Tyr Arg Lys Glu Tyr Glu Gly Glu Ala Ile Leu
 355 360 365
 Trp Gln Arg Ser Ala Ala Glu Asp Gln Arg Thr Ser Thr Tyr Asn Gly
 370 375 380
 Asp Ile Arg Glu Thr Arg Thr Asp Gln Glu Asn Lys Asp Pro Asn Pro
 385 390 395 400
 Arg Leu Glu Lys Pro Val Leu Leu Ser Glu Phe Pro Thr Lys Ile Pro
 405 410 415

Arg Gly Glu Leu Asp Met Pro Val Glu Asn Gly Leu Arg Ala Pro Val
 420 425 430

Ser Ala Tyr Gln Tyr Ala Leu Ala Asn Gly Asp Val Trp Lys Val His
 435 440 445

Glu Val Pro Asp Tyr Ser Met Ala Tyr Gly Asn Pro Gly Val Ala Asp
 450 455 460

Ala Thr Pro Pro Trp Ser Ser Tyr Lys Glu Gln Ser Pro Gln Thr Leu
 465 470 475 480

Leu Glu Leu Lys Arg Gln Arg Ala Ala Ala Lys Leu Leu Ser His Pro
 485 490 495

Phe Leu Ser Thr His Leu Gly Ser Ser Met Ala Arg Thr Gly Glu Ser
 500 505 510

Ser Ser Glu Gly Lys Ala Pro Leu Ile Gly Gly Arg Thr Ser Pro Tyr
 515 520 525

Ser Ser Asn Gly Thr Ser Val Tyr Tyr Thr Val Thr Ser Gly Asp Pro
 530 535 540

Pro Leu Leu Lys Phe Lys Ala Pro Ile Glu Glu Met Glu Glu Lys Val
 545 550 555 560

His Gly Cys Cys Arg Ile Ser
 565

<210> 100
 <211> 380
 <212> PRT
 <213> Homo sapiens

<400> 100

Met Leu Arg Arg Lys Pro Ser Asn Ala Ser Glu Lys Glu Pro Thr Gln
 1 5 10 15

Lys Lys Lys Leu Ser Leu Gln Arg Ser Ser Ser Phe Lys Asp Phe Ala
 20 25 30

Lys Ser Lys Pro Ser Ser Pro Val Val Ser Glu Lys Glu Phe Asn Leu
 35 40 45

Asp Asp Asn Ile Pro Glu Asp Asp Ser Gly Val Pro Thr Pro Glu Asp
 50 55 60

Ala Gly Lys Ser Gly Lys Lys Leu Gly Lys Lys Trp Arg Ala Val Ile
 65 70 75 80

Ser Arg Thr Met Asn Arg Lys Met Gly Lys Met Met Val Lys Ala Leu
 85 90 95

Ser Glu Glu Met Ala Asp Thr Leu Glu Glu Gly Ser Ala Ser Pro Thr
 100 105 110

Ser Pro Asp Tyr Ser Leu Asp Ser Pro Gly Pro Glu Lys Met Ala Leu
 115 120 125

Ala Phe Ser Glu Gln Glu Glu His Glu Leu Pro Val Leu Ser Arg Gln
 130 135 140

Ala Ser Thr Gly Ser Glu Leu Cys Ser Pro Ser Pro Gly Ser Gly Ser
 145 150 155 160

Phe Gly Glu Glu Pro Pro Ala Pro Gln Tyr Thr Gly Pro Phe Cys Gly
 165 170 175

Arg Ala Arg Val His Thr Asp Phe Thr Pro Ser Pro Tyr Asp His Asp
 180 185 190

Ser Leu Lys Leu Gln Lys Gly Asp Val Ile Gln Ile Ile Glu Lys Pro
 195 200 205

Pro Val Gly Thr Trp Leu Gly Leu Leu Asn Gly Lys Val Gly Ser Phe
 210 215 220

Lys Phe Ile Tyr Val Asp Val Leu Pro Glu Glu Ala Val Gly His Ala
 225 230 235 240

Arg Pro Ser Arg Arg Gln Ser Lys Gly Lys Arg Pro Lys Pro Lys Thr
 245 250 255

Leu His Glu Leu Leu Glu Arg Ile Gly Leu Glu Glu His Thr Ser Thr
 260 265 270

Leu Leu Leu Asn Gly Tyr Gln Thr Leu Glu Asp Phe Lys Glu Leu Arg
 275 280 285

Glu Thr His Leu Asn Glu Leu Asn Ile Met Asp Pro Gln His Arg Ala
 290 295 300

Lys Leu Leu Thr Ala Ala Glu Leu Leu Leu Asp Tyr Asp Thr Gly Ser

305 310 315 320

Glu Glu Ala Glu Glu Gly Ala Glu Ser Ser Gln Glu Pro Val Ala His
325 330 335

Thr Val Ser Glu Pro Lys Val Asp Ile Pro Arg Asp Ser Gly Cys Phe
340 345 350

Glu Gly Ser Glu Ser Gly Arg Asp Asp Ala Glu Leu Ala Gly Thr Glu
355 360 365

Glu Gln Leu Gln Gly Leu Ser Leu Ala Gly Ala Pro
370 375 380

<210> 101
<211> 1247
<212> PRT
<213> Homo sapiens
<400> 101

Met Glu Asp Ala Gly Ala Ala Gly Pro Gly Pro Glu Pro Glu Pro Glu
1 5 10 15

Pro Glu Pro Glu Pro Glu Pro Ala Pro Glu Pro Glu Pro Glu Pro Lys
20 25 30

Pro Gly Ala Gly Thr Ser Glu Ala Phe Ser Arg Leu Trp Thr Asp Val
35 40 45

Met Gly Ile Leu Asp Gly Ser Leu Gly Asn Ile Asp Asp Leu Ala Gln
50 55 60

Gln Tyr Ala Asp Tyr Tyr Asn Thr Cys Phe Ser Asp Val Cys Glu Arg
65 70 75 80

Met Glu Glu Leu Arg Lys Arg Arg Val Ser Gln Asp Leu Glu Val Glu
85 90 95

Lys Pro Asp Ala Ser Pro Thr Ser Leu Gln Leu Arg Ser Gln Ile Glu
100 105 110

Glu Ser Leu Gly Phe Cys Ser Ala Val Ser Thr Pro Glu Val Glu Arg
115 120 125

Lys Asn Pro Leu His Lys Ser Asn Ser Glu Asp Ser Ser Val Gly Lys
130 135 140

Gly Asp Trp Lys Lys Lys Asn Lys Tyr Phe Trp Gln Asn Phe Arg Lys
 145 150 155 160

Asn Gln Lys Gly Ile Met Arg Gln Thr Ser Lys Gly Glu Asp Val Gly
 165 170 175

Tyr Val Ala Ser Glu Ile Thr Met Ser Asp Glu Glu Arg Ile Gln Leu
 180 185 190

Met Met Met Val Lys Glu Lys Met Ile Thr Ile Glu Glu Ala Leu Ala
 195 200 205

Arg Leu Lys Glu Tyr Glu Ala Gln His Arg Gln Ser Ala Ala Leu Asp
 210 215 220

Pro Ala Asp Trp Pro Asp Gly Ser Tyr Pro Thr Phe Asp Gly Ser Ser
 225 230 235 240

Asn Cys Asn Ser Arg Glu Gln Ser Asp Asp Glu Thr Glu Glu Ser Val
 245 250 255

Lys Phe Lys Arg Leu His Lys Leu Val Asn Ser Thr Arg Arg Val Arg
 260 265 270

Lys Lys Leu Ile Arg Val Glu Glu Met Lys Lys Pro Ser Thr Glu Gly
 275 280 285

Gly Glu Glu His Val Phe Glu Asn Ser Pro Val Leu Asp Glu Arg Ser
 290 295 300

Ala Leu Tyr Ser Gly Val His Lys Lys Pro Leu Phe Phe Asp Gly Ser
 305 310 315 320

Pro Glu Lys Pro Pro Glu Asp Asp Ser Asp Ser Leu Thr Thr Ser Pro
 325 330 335

Ser Ser Ser Ser Leu Asp Thr Trp Gly Ala Gly Arg Lys Leu Val Lys
 340 345 350

Thr Phe Ser Lys Gly Glu Ser Arg Gly Leu Ile Lys Pro Pro Lys Lys
 355 360 365

Met Gly Thr Phe Phe Ser Tyr Pro Glu Glu Glu Lys Ala Gln Lys Val
 370 375 380

Ser Arg Ser Leu Thr Glu Gly Glu Met Lys Lys Gly Leu Gly Ser Leu
 385 390 395 400

Ser His Gly Arg Thr Cys Ser Phe Gly Gly Phe Asp Leu Thr Asn Arg
 405 410 415

Ser Leu His Val Gly Ser Asn Asn Ser Asp Pro Met Gly Lys Glu Gly
 420 425 430

Asp Phe Val Tyr Lys Glu Val Ile Lys Ser Pro Thr Ala Ser Arg Ile
 435 440 445

Ser Leu Gly Lys Lys Val Lys Ser Val Lys Glu Thr Met Arg Lys Arg
 450 455 460

Met Ser Lys Lys Tyr Ser Ser Ser Val Ser Glu Gln Asp Ser Gly Leu
 465 470 475 480

Asp Gly Met Pro Gly Ser Pro Pro Pro Ser Gln Pro Asp Pro Glu His
 485 490 495

Leu Asp Lys Pro Lys Leu Lys Ala Gly Gly Ser Val Glu Ser Leu Arg
 500 505 510

Ser Ser Leu Ser Gly Gln Ser Ser Met Ser Gly Gln Thr Val Ser Thr
 515 520 525

Thr Asp Ser Ser Thr Ser Asn Arg Glu Ser Val Lys Ser Glu Asp Gly
 530 535 540

Asp Asp Glu Glu Pro Pro Tyr Arg Gly Pro Phe Cys Gly Arg Ala Arg
 545 550 555 560

Val His Thr Asp Phe Thr Pro Ser Pro Tyr Asp Thr Asp Ser Leu Lys
 565 570 575

Leu Lys Lys Gly Asp Ile Ile Asp Ile Ile Ser Lys Pro Pro Met Gly
 580 585 590

Thr Trp Met Gly Leu Leu Asn Asn Lys Val Gly Thr Phe Lys Phe Ile
 595 600 605

Tyr Val Asp Val Leu Ser Glu Asp Glu Glu Lys Pro Lys Arg Pro Thr
 610 615 620

Arg Arg Arg Arg Lys Gly Arg Pro Pro Gln Pro Lys Ser Val Glu Asp
 625 630 635 640

Leu Leu Asp Arg Ile Asn Leu Lys Glu His Met Pro Thr Phe Leu Phe
 645 650 655
 Asn Gly Tyr Glu Asp Leu Asp Thr Phe Lys Leu Leu Glu Glu Glu Asp
 660 665 670
 Leu Asp Glu Leu Asn Ile Arg Asp Pro Glu His Arg Ala Val Leu Leu
 675 680 685
 Thr Ala Val Glu Leu Leu Gln Glu Tyr Asp Ser Asn Ser Asp Gln Ser
 690 695 700
 Gly Ser Gln Glu Lys Leu Leu Val Asp Ser Gln Gly Leu Ser Gly Cys
 705 710 715 720
 Ser Pro Arg Asp Ser Gly Cys Tyr Glu Ser Ser Glu Asn Leu Glu Asn
 725 730 735
 Gly Lys Thr Arg Lys Ala Ser Leu Leu Ser Ala Lys Ser Ser Thr Glu
 740 745 750
 Pro Ser Leu Lys Ser Phe Ser Arg Asn Gln Leu Gly Asn Tyr Pro Thr
 755 760 765
 Leu Pro Leu Met Lys Ser Gly Asp Ala Leu Lys Gln Gly Gln Glu Glu
 770 775 780
 Gly Arg Leu Gly Gly Gly Leu Ala Pro Asp Thr Ser Lys Ser Cys Asp
 785 790 795 800
 Pro Pro Gly Val Thr Gly Leu Asn Lys Asn Arg Arg Ser Leu Pro Val
 805 810 815
 Ser Ile Cys Arg Ser Cys Glu Thr Leu Glu Gly Pro Gln Thr Val Asp
 820 825 830
 Thr Trp Pro Arg Ser His Ser Leu Asp Asp Leu Gln Val Glu Pro Gly
 835 840 845
 Ala Glu Gln Asp Val Pro Thr Glu Val Thr Glu Pro Pro Pro Gln Ile
 850 855 860
 Val Pro Glu Val Pro Gln Lys Thr Thr Ala Ser Ser Thr Lys Ala Gln
 865 870 875 880
 Pro Leu Glu Gln Asp Ser Ala Val Asp Asn Ala Leu Leu Leu Thr Gln
 885 890 895

Ser Lys Arg Phe Ser Glu Pro Gln Lys Leu Thr Thr Lys Lys Leu Glu
 900 905 910

Gly Ser Ile Ala Ala Ser Gly Arg Gly Leu Ser Pro Pro Gln Cys Leu
 915 920 925

Pro Arg Asn Tyr Asp Ala Gln Pro Pro Gly Ala Lys His Gly Leu Ala
 930 935 940

Arg Thr Pro Leu Glu Gly His Arg Lys Gly His Glu Phe Glu Gly Thr
 945 950 955 960

His His Pro Leu Gly Thr Lys Glu Gly Val Asp Ala Glu Gln Arg Met
 965 970 975

Gln Pro Lys Ile Pro Ser Gln Pro Pro Pro Val Pro Ala Lys Lys Ser
 980 985 990

Arg Glu Arg Leu Ala Asn Gly Leu His Pro Val Pro Met Gly Pro Ser
 995 1000 1005

Gly Ala Leu Pro Ser Pro Asp Ala Pro Cys Leu Pro Val Lys Arg
 1010 1015 1020

Gly Ser Pro Ala Ser Pro Thr Ser Pro Ser Asp Cys Pro Pro Ala
 1025 1030 1035

Leu Ala Pro Arg Pro Leu Ser Gly Gln Ala Pro Gly Ser Pro Pro
 1040 1045 1050

Ser Thr Arg Pro Pro Pro Trp Leu Ser Glu Leu Pro Glu Asn Thr
 1055 1060 1065

Ser Leu Gln Glu His Gly Val Lys Leu Gly Pro Ala Leu Thr Arg
 1070 1075 1080

Lys Val Ser Cys Ala Arg Gly Val Asp Leu Glu Thr Leu Thr Glu
 1085 1090 1095

Asn Lys Leu His Ala Glu Gly Ile Asp Leu Thr Glu Glu Pro Tyr
 1100 1105 1110

Ser Asp Lys His Gly Arg Cys Gly Ile Pro Glu Ala Leu Val Gln
 1115 1120 1125

Arg Tyr Ala Glu Asp Leu Asp Gln Pro Glu Arg Asp Val Ala Ala
1130 1135 1140

Asn Met Asp Gln Ile Arg Val Lys Gln Leu Arg Lys Gln His Arg
1145 1150 1155

Met Ala Ile Pro Ser Gly Gly Leu Thr Glu Ile Cys Arg Lys Pro
1160 1165 1170

Val Ser Pro Gly Cys Ile Ser Ser Val Ser Asp Trp Leu Ile Ser
1175 1180 1185

Ile Gly Leu Pro Met Tyr Ala Gly Thr Leu Ser Thr Ala Gly Phe
1190 1195 1200

Ser Thr Leu Ser Gln Val Pro Ser Leu Ser His Thr Cys Leu Gln
1205 1210 1215

Glu Ala Gly Ile Thr Glu Glu Arg His Ile Arg Lys Leu Leu Ser
1220 1225 1230

Ala Ala Arg Leu Phe Lys Leu Pro Pro Gly Pro Glu Ala Met
1235 1240 1245

<210> 102
<211> 373
<212> PRT
<213> Homo sapiens

<400> 102

Met Leu Lys Arg Lys Pro Ser Asn Val Ser Glu Lys Glu Lys His Gln
1 5 10 15

Lys Pro Lys Arg Ser Ser Ser Phe Gly Asn Phe Asp Arg Phe Arg Asn
20 25 30

Asn Ser Leu Ser Lys Pro Asp Asp Ser Thr Glu Ala His Glu Gly Asp
35 40 45

Pro Thr Asn Gly Ser Gly Glu Gln Ser Lys Thr Ser Asn Asn Gly Gly
50 55 60

Gly Leu Gly Lys Lys Met Arg Ala Ile Ser Trp Thr Met Lys Lys Lys
65 70 75 80

Val Gly Lys Lys Tyr Ile Lys Ala Leu Ser Glu Glu Lys Asp Glu Glu
85 90 95

Asp Gly Glu Asn Ala His Pro Tyr Arg Asn Ser Asp Pro Val Ile Gly
 100 105 110
 Thr His Thr Glu Lys Val Ser Leu Lys Ala Ser Asp Ser Met Asp Ser
 115 120 125
 Leu Tyr Ser Gly Gln Ser Ser Ser Ser Gly Ile Thr Ser Cys Ser Asp
 130 135 140
 Gly Thr Ser Asn Arg Asp Ser Phe Arg Leu Asp Asp Asp Gly Pro Tyr
 145 150 155 160
 Ser Gly Pro Phe Cys Gly Arg Ala Arg Val His Thr Asp Phe Thr Pro
 165 170 175
 Ser Pro Tyr Asp Thr Asp Ser Leu Lys Ile Lys Lys Gly Asp Ile Ile
 180 185 190
 Asp Ile Ile Cys Lys Thr Pro Met Gly Met Trp Thr Gly Met Leu Asn
 195 200 205
 Asn Lys Val Gly Asn Phe Lys Phe Ile Tyr Val Asp Val Ile Ser Glu
 210 215 220
 Glu Glu Ala Ala Pro Lys Lys Ile Lys Ala Asn Arg Arg Ser Asn Ser
 225 230 235 240
 Lys Lys Ser Lys Thr Leu Gln Glu Phe Leu Glu Arg Ile His Leu Gln
 245 250 255
 Glu Tyr Thr Ser Thr Leu Leu Leu Asn Gly Tyr Glu Thr Leu Glu Asp
 260 265 270
 Leu Lys Asp Ile Lys Glu Ser His Leu Ile Glu Leu Asn Ile Glu Asn
 275 280 285
 Pro Asp Asp Arg Arg Arg Leu Leu Ser Ala Ala Glu Asn Phe Leu Glu
 290 295 300
 Glu Glu Ile Ile Gln Glu Gln Glu Asn Glu Pro Glu Pro Leu Ser Leu
 305 310 315 320
 Ser Ser Asp Ile Ser Leu Asn Lys Ser Gln Leu Asp Asp Cys Pro Arg
 325 330 335
 Asp Ser Gly Cys Tyr Ile Ser Ser Gly Asn Ser Asp Asn Gly Lys Glu

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      340                      345                      350
Asp Leu Glu Ser Glu Asn Leu Ser Asp Met Val His Lys Ile Ile Ile
    355                               360                       365

Thr Glu Pro Ser Asp
   370

<210> 103
<211> 431
<212> PRT
<213> Homo sapiens

<400> 103

Met Glu Gly Ser Ala Ser Pro Pro Glu Lys Pro Arg Ala Arg Pro Ala
 1                                10                            15

Ala Ala Val Leu Cys Arg Gly Pro Val Glu Pro Leu Val Phe Leu Ala
           20                              25                          30

Asn Phe Ala Leu Val Leu Gln Gly Pro Leu Thr Thr Gln Tyr Leu Trp
   35                                  40                             45

His Arg Phe Ser Ala Asp Leu Gly Tyr Asn Gly Thr Arg Gln Arg Gly
   50                                   55                             60

Gly Cys Ser Asn Arg Ser Ala Asp Pro Thr Met Gln Glu Val Glu Thr
 65                                     70                         75              80

Leu Thr Ser His Trp Thr Leu Tyr Met Asn Val Gly Gly Phe Leu Val
            85                                 90                        95

Gly Leu Phe Ser Ser Thr Leu Leu Gly Ala Trp Ser Asp Ser Val Gly
          100                               105                     110

Arg Arg Pro Leu Leu Val Leu Ala Ser Leu Gly Leu Leu Leu Gln Ala
       115                               120                           125

Leu Val Ser Val Phe Val Val Gln Leu Gln Leu His Val Gly Tyr Phe
   130                135                    140

Val Leu Gly Arg Ile Leu Cys Ala Leu Leu Gly Asp Phe Gly Gly Leu
 145                 150                   155               160

Leu Ala Ala Ser Phe Ala Ser Val Ala Asp Val Ser Ser Ser Arg Ser
        165                               170                     175
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Arg Thr Phe Arg Met Ala Leu Leu Glu Ala Ser Ile Gly Val Ala Gly
 180 185 190

Met Leu Ala Ser Leu Leu Gly Gly His Trp Leu Arg Ala Gln Gly Tyr
 195 200 205

Ala Asn Pro Phe Trp Leu Ala Leu Ala Leu Leu Ile Ala Met Thr Leu
 210 215 220

Tyr Ala Ala Phe Cys Phe Gly Glu Thr Leu Lys Glu Pro Lys Ser Thr
 225 230 235 240

Arg Leu Phe Thr Phe Arg His His Arg Ser Ile Val Gln Leu Tyr Val
 245 250 255

Ala Pro Ala Pro Glu Lys Ser Arg Lys His Leu Ala Leu Tyr Ser Leu
 260 265 270

Ala Ile Phe Val Val Ile Thr Val His Phe Gly Ala Gln Asp Ile Leu
 275 280 285

Thr Leu Tyr Glu Leu Ser Thr Pro Leu Cys Trp Asp Ser Lys Leu Ile
 290 295 300

Gly Tyr Gly Ser Ala Ala Gln His Leu Pro Tyr Leu Thr Ser Leu Leu
 305 310 315 320

Ala Leu Lys Leu Leu Gln Tyr Cys Leu Ala Asp Ala Trp Val Ala Glu
 325 330 335

Ile Gly Leu Ala Phe Asn Ile Leu Gly Met Val Val Phe Ala Phe Ala
 340 345 350

Thr Ile Thr Pro Leu Met Phe Thr Gly Ala Leu Phe Ser Ala Val Ala
 355 360 365

Cys Val Asn Ser Leu Ala Met Leu Thr Ala Ser Gly Ile Phe Asn Ser
 370 375 380

Leu Tyr Pro Ala Thr Leu Asn Phe Met Lys Gly Phe Pro Phe Leu Leu
 385 390 395 400

Gly Ala Gly Leu Leu Leu Ile Pro Ala Val Leu Ile Gly Met Leu Glu
 405 410 415

Lys Ala Asp Pro His Leu Glu Phe Gln Gln Phe Pro Gln Ser Pro
 420 425 430

<210> 104
 <211> 463
 <212> PRT
 <213> Homo sapiens

<400> 104

Met Lys Ile Leu Phe Val Glu Pro Ala Ile Phe Leu Ser Ala Phe Ala
 1 5 10 15

Met Thr Leu Thr Gly Pro Leu Thr Thr Gln Tyr Val Tyr Arg Arg Ile
 20 25 30

Trp Glu Glu Thr Gly Asn Tyr Thr Phe Ser Ser Asp Ser Asn Ile Ser
 35 40 45

Glu Cys Glu Lys Asn Lys Ser Ser Pro Ile Phe Ala Phe Gln Glu Glu
 50 55 60

Val Gln Lys Lys Val Ser Arg Phe Asn Leu Gln Met Asp Ile Ser Gly
 65 70 75 80

Leu Ile Pro Gly Leu Val Ser Thr Phe Ile Leu Leu Ser Ile Ser Asp
 85 90 95

His Tyr Gly Arg Lys Phe Pro Met Ile Leu Ser Ser Val Gly Ala Leu
 100 105 110

Ala Thr Ser Val Trp Leu Cys Leu Leu Cys Tyr Phe Ala Leu Pro Phe
 115 120 125

Gln Leu Leu Ile Ala Ser Thr Phe Ile Gly Ala Ile Cys Gly Asn Tyr
 130 135 140

Thr Thr Phe Trp Gly Ala Cys Phe Ala Tyr Ile Val Asp Gln Cys Lys
 145 150 155 160

Glu His Lys Gln Lys Thr Ile Arg Ile Ala Ile Ile Asp Phe Leu Leu
 165 170 175

Gly Leu Val Thr Gly Leu Thr Gly Leu Ser Ser Gly Tyr Phe Ile Arg
 180 185 190

Glu Leu Gly Phe Glu Trp Ser Phe Leu Ile Ile Ala Val Ser Leu Ala
 195 200 205

Val Asn Leu Ile Tyr Ile Leu Phe Phe Leu Gly Asp Pro Val Lys Glu

210	215	220
Cys Ser Ser Gln Asn Val Thr Met Ser Cys Ser Glu Gly Phe Lys Asn		
225	230	235 240
Leu Phe Tyr Arg Thr Tyr Met Leu Phe Lys Asn Ala Ser Gly Lys Arg		
	245	250 255
Arg Phe Leu Leu Cys Leu Leu Leu Phe Thr Val Ile Thr Tyr Phe Phe		
	260	265 270
Val Val Ile Gly Ile Ala Pro Ile Phe Ile Leu Tyr Glu Leu Asp Ser		
	275	280 285
Pro Leu Cys Trp Asn Glu Val Phe Ile Gly Tyr Gly Ser Ala Leu Gly		
	290	295 300
Ser Ala Ser Phe Leu Thr Ser Phe Leu Gly Ile Trp Leu Phe Ser Tyr		
305	310	315 320
Cys Met Glu Asp Ile His Met Ala Phe Ile Gly Ile Phe Thr Thr Met		
	325	330 335
Thr Gly Met Ala Met Thr Ala Phe Ala Ser Thr Thr Leu Met Met Phe		
	340	345 350
Leu Ala Arg Val Pro Phe Leu Phe Thr Ile Val Pro Phe Ser Val Leu		
	355	360 365
Arg Ser Met Leu Ser Lys Val Val Arg Ser Thr Glu Gln Gly Thr Leu		
	370	375 380
Phe Ala Cys Ile Ala Phe Leu Glu Thr Leu Gly Gly Val Thr Ala Val		
385	390	395 400
Ser Thr Phe Asn Gly Ile Tyr Ser Ala Thr Val Ala Trp Tyr Pro Gly		
	405	410 415
Phe Thr Phe Leu Leu Ser Ala Gly Leu Leu Leu Leu Pro Ala Ile Ser		
	420	425 430
Leu Cys Val Val Lys Cys Thr Ser Trp Asn Glu Gly Ser Tyr Glu Leu		
	435	440 445
Leu Ile Gln Glu Glu Ser Ser Glu Asp Ala Ser Asp Arg Ala Cys		
450	455	460

<210> 105

<211> 575

<212> PRT

<213> Homo sapiens

<400> 105

Met Ser Ala Ala Thr His Ser Pro Met Met Gln Val Ala Ser Gly Asn
 1 5 10 15

Gly Asp Arg Asp Pro Leu Pro Pro Gly Trp Glu Ile Lys Ile Asp Pro
 20 25 30

Gln Thr Gly Trp Pro Phe Phe Val Asp His Asn Ser Arg Thr Thr Thr
 35 40 45

Trp Asn Asp Pro Arg Val Pro Ser Glu Gly Pro Lys Glu Thr Pro Ser
 50 55 60

Ser Ala Asn Gly Pro Ser Arg Glu Gly Ser Arg Leu Pro Pro Ala Arg
 65 70 75 80

Glu Gly His Pro Val Tyr Pro Gln Leu Arg Pro Gly Tyr Ile Pro Ile
 85 90 95

Pro Val Leu His Glu Gly Ala Glu Asn Arg Gln Val His Pro Phe His
 100 105 110

Val Tyr Pro Gln Pro Gly Met Gln Arg Phe Arg Thr Glu Ala Ala Ala
 115 120 125

Ala Ala Pro Gln Arg Ser Gln Ser Pro Leu Arg Gly Met Pro Glu Thr
 130 135 140

Thr Gln Pro Asp Lys Gln Cys Gly Gln Val Ala Ala Ala Ala Ala Ala
 145 150 155 160

Gln Pro Pro Ala Ser His Gly Pro Glu Arg Ser Gln Ser Pro Ala Ala
 165 170 175

Ser Asp Cys Ser Ser Ser Ser Ser Ser Ala Ser Leu Pro Ser Ser Gly
 180 185 190

Arg Ser Ser Leu Gly Ser His Gln Leu Pro Arg Gly Tyr Ile Ser Ile
 195 200 205

Pro Val Ile His Glu Gln Asn Val Thr Arg Pro Ala Ala Gln Pro Ser
 210 215 220

Phe His Gln Ala Gln Lys Thr His Tyr Pro Ala Gln Gln Gly Glu Tyr
 225 230 235 240

Gln Thr His Gln Pro Val Tyr His Lys Ile Gln Gly Asp Asp Trp Glu
 245 250 255

Pro Arg Pro Leu Arg Ala Ala Ser Pro Phe Arg Ser Ser Val Gln Gly
 260 265 270

Ala Ser Ser Arg Glu Gly Ser Pro Ala Arg Ser Ser Thr Pro Leu His
 275 280 285

Ser Pro Ser Pro Ile Arg Val His Thr Val Val Asp Arg Pro Gln Gln
 290 295 300

Pro Met Thr His Arg Glu Thr Ala Pro Val Ser Gln Pro Glu Asn Lys
 305 310 315 320

Pro Glu Ser Lys Pro Gly Pro Val Gly Pro Glu Leu Pro Pro Gly His
 325 330 335

Ile Pro Ile Gln Val Ile Arg Lys Glu Val Asp Ser Lys Pro Val Ser
 340 345 350

Gln Lys Pro Pro Pro Pro Ser Glu Lys Val Glu Val Lys Val Pro Pro
 355 360 365

Ala Pro Val Pro Cys Pro Pro Pro Ser Pro Gly Pro Ser Ala Val Pro
 370 375 380

Ser Ser Pro Lys Ser Val Ala Thr Glu Glu Arg Ala Ala Pro Ser Thr
 385 390 395 400

Ala Pro Ala Glu Ala Thr Pro Pro Lys Pro Gly Glu Ala Glu Ala Pro
 405 410 415

Pro Lys His Pro Gly Val Leu Lys Val Glu Ala Ile Leu Glu Lys Val
 420 425 430

Gln Gly Leu Glu Gln Ala Val Asp Asn Phe Glu Gly Lys Lys Thr Asp
 435 440 445

Lys Lys Tyr Leu Met Ile Glu Glu Tyr Leu Thr Lys Glu Leu Leu Ala
 450 455 460

Leu Asp Ser Val Asp Pro Glu Gly Arg Ala Asp Val Arg Gln Ala Arg
 465 470 475 480

Arg Asp Gly Val Arg Lys Val Gln Thr Ile Leu Glu Lys Leu Glu Gln
 485 490 495

Lys Ala Ile Asp Val Pro Gly Gln Val Gln Val Tyr Glu Leu Gln Pro
 500 505 510

Ser Asn Leu Glu Ala Asp Gln Pro Leu Gln Ala Ile Met Glu Met Gly
 515 520 525

Ala Val Ala Ala Asp Lys Gly Lys Lys Asn Ala Gly Asn Ala Glu Asp
 530 535 540

Pro His Thr Glu Thr Gln Gln Pro Glu Ala Thr Ala Ala Ala Thr Ser
 545 550 555 560

Asn Pro Ser Ser Met Thr Asp Thr Pro Gly Asn Pro Ala Ala Pro
 565 570 575

<210> 106
 <211> 457
 <212> PRT
 <213> Homo sapiens

<400> 106

Met Ser Ala Leu Arg Arg Ser Gly Tyr Gly Pro Ser Asp Gly Pro Ser
 1 5 10 15

Tyr Gly Arg Tyr Tyr Gly Pro Gly Gly Gly Asp Val Pro Val His Pro
 20 25 30

Pro Pro Pro Leu Tyr Pro Leu Arg Pro Glu Pro Pro Gln Pro Pro Ile
 35 40 45

Ser Trp Arg Val Arg Gly Gly Gly Pro Ala Glu Thr Thr Trp Leu Gly
 50 55 60

Glu Gly Gly Gly Gly Asp Gly Tyr Tyr Pro Ser Gly Gly Ala Trp Pro
 65 70 75 80

Glu Pro Gly Arg Ala Gly Gly Ser His Gln Glu Gln Pro Pro Tyr Pro
 85 90 95

Ser Tyr Asn Ser Asn Tyr Trp Asn Ser Thr Ala Arg Ser Arg Ala Pro
 100 105 110

Tyr Pro Ser Thr Tyr Pro Val Arg Pro Glu Leu Gln Gly Gln Ser Leu
 115 120 125

Asn Ser Tyr Thr Asn Gly Ala Tyr Gly Pro Thr Tyr Pro Pro Gly Pro
 130 135 140

Gly Ala Asn Thr Ala Ser Tyr Ser Gly Ala Tyr Tyr Ala Pro Gly Tyr
 145 150 155 160

Thr Gln Thr Ser Tyr Ser Thr Glu Val Pro Ser Thr Tyr Arg Ser Ser
 165 170 175

Gly Asn Ser Pro Thr Pro Val Ser Arg Trp Ile Tyr Pro Gln Gln Asp
 180 185 190

Cys Gln Thr Glu Ala Pro Pro Leu Arg Gly Gln Val Pro Gly Tyr Pro
 195 200 205

Pro Ser Gln Asn Pro Gly Met Thr Leu Pro His Tyr Pro Tyr Gly Asp
 210 215 220

Gly Asn Arg Ser Val Pro Gln Ser Gly Pro Thr Val Arg Pro Gln Glu
 225 230 235 240

Asp Ala Trp Ala Ser Pro Gly Ala Tyr Gly Met Gly Gly Arg Tyr Pro
 245 250 255

Trp Pro Ser Ser Ala Pro Ser Ala Pro Pro Gly Asn Leu Tyr Met Thr
 260 265 270

Glu Ser Thr Ser Pro Trp Pro Ser Ser Gly Ser Pro Gln Ser Pro Pro
 275 280 285

Ser Pro Pro Val Gln Gln Pro Lys Asp Ser Ser Tyr Pro Tyr Ser Gln
 290 295 300

Ser Asp Gln Ser Met Asn Arg His Asn Phe Pro Cys Ser Val His Gln
 305 310 315 320

Tyr Glu Ser Ser Gly Thr Val Asn Asn Asp Asp Ser Asp Leu Leu Asp
 325 330 335

Ser Gln Val Gln Tyr Ser Ala Glu Pro Gln Leu Tyr Gly Asn Ala Thr
 340 345 350

Ser Asp His Pro Asn Asn Gln Asp Gln Ser Ser Ser Leu Pro Glu Glu

355 360 365
 Cys Val Pro Ser Asp Glu Ser Thr Pro Pro Ser Ile Lys Lys Ile Ile
 370 375 380
 His Val Leu Glu Lys Val Gln Tyr Leu Glu Gln Glu Val Glu Glu Phe
 385 390 395 400
 Val Gly Lys Lys Thr Asp Lys Ala Tyr Trp Leu Leu Glu Glu Met Leu
 405 410 415
 Thr Lys Glu Leu Leu Glu Leu Asp Ser Val Glu Thr Gly Gly Gln Asp
 420 425 430
 Ser Val Arg Gln Ala Arg Lys Glu Ala Val Cys Lys Ile Gln Ala Ile
 435 440 445
 \
 Leu Glu Lys Leu Glu Lys Lys Gly Leu
 450 455

 <210> 107
 <211> 373
 <212> PRT
 <213> Homo sapiens

 <400> 107
 Met Ala Gln Gly Arg Glu Arg Asp Glu Gly Pro His Ser Ala Gly Gly
 1 5 10 15
 Ala Ser Leu Ser Val Arg Trp Val Gln Gly Phe Pro Lys Gln Asn Val
 20 25 30
 His Phe Val Asn Asp Asn Thr Ile Cys Tyr Pro Cys Gly Asn Tyr Val
 35 40 45
 Ile Phe Ile Asn Ile Glu Thr Lys Lys Lys Thr Val Leu Gln Cys Ser
 50 55 60
 Asn Gly Ile Val Gly Val Met Ala Thr Asn Ile Pro Cys Glu Val Val
 65 70 75 80
 Ala Phe Ser Asp Arg Lys Leu Lys Pro Leu Ile Tyr Val Tyr Ser Phe
 85 90 95
 Pro Gly Leu Thr Arg Arg Thr Lys Leu Lys Gly Asn Ile Leu Leu Asp
 100 105 110

Tyr Thr Leu Leu Ser Phe Ser Tyr Cys Gly Thr Tyr Leu Ala Ser Tyr
 115 120 125

Ser Ser Leu Pro Glu Phe Glu Leu Ala Leu Trp Asn Trp Glu Ser Ser
 130 135 140

Ile Ile Leu Cys Lys Lys Ser Gln Pro Gly Met Asp Val Asn Glu Met
 145 150 155 160

Ser Phe Asn Pro Met Asn Trp Arg Gln Leu Cys Leu Ser Ser Pro Ser
 165 170 175

Thr Val Ser Val Trp Thr Ile Glu Arg Ser Asn Gln Glu His Cys Phe
 180 185 190

Arg Ala Arg Ser Val Lys Leu Pro Leu Glu Asp Gly Ser Phe Phe Asn
 195 200 205

Glu Thr Asp Val Val Phe Pro Gln Ser Leu Pro Lys Asp Leu Ile Tyr
 210 215 220

Gly Pro Val Leu Pro Leu Ser Ala Ile Ala Gly Leu Val Gly Lys Glu
 225 230 235 240

Ala Glu Thr Phe Arg Pro Lys Asp Asp Leu Tyr Pro Leu Leu His Pro
 245 250 255

Thr Met His Cys Trp Thr Pro Thr Ser Asp Leu Tyr Ile Gly Cys Glu
 260 265 270

Glu Gly His Leu Leu Met Ile Asn Gly Asp Thr Leu Gln Val Thr Val
 275 280 285

Leu Asn Lys Ile Glu Glu Glu Ser Pro Leu Glu Asp Arg Arg Asn Phe
 290 295 300

Ile Ser Pro Val Thr Leu Val Tyr Gln Lys Glu Gly Val Leu Ala Ser
 305 310 315 320

Gly Ile Asp Gly Phe Val Tyr Ser Phe Ile Ile Lys Asp Arg Ser Tyr
 325 330 335

Met Ile Glu Asp Phe Leu Glu Ile Glu Arg Pro Val Glu His Met Thr
 340 345 350

Phe Ser Pro Asn Tyr Thr Val Leu Leu Ile Gln Thr Asp Lys Val Cys
 355 360 365

Trp Met Val Ile Ser
370

<210> 108
<211> 401
<212> PRT
<213> Homo sapiens

<400> 108

Met Lys Leu Ser Asp Leu His His Val Thr Leu Phe Gln Glu Ile Leu
1 5 10 15

Leu Leu Lys Asn Phe Glu Lys Gln Glu Asn Ile Leu Gln Glu Arg Val
20 25 30

Asn Ser Leu Asp Lys Glu Glu Gln Tyr Met Gln Trp Lys Ile Asn Glu
35 40 45

Thr Leu Lys Glu Met Glu Glu Lys Lys Asn Glu Ile Thr Lys Leu Gln
50 55 60

Glu Gln Glu Lys Ala Leu Tyr Ala Gly Phe Gln Ala Ala Ile Gly Glu
65 70 75 80

Asn Asn Lys Phe Ala Asn Phe Leu Met Lys Val Leu Lys Lys Arg Ile
85 90 95

Lys Arg Val Lys Lys Lys Glu Val Glu Gly Asp Ala Asp Glu Asp Glu
100 105 110

Glu Ser Glu Glu Ser Ser Glu Glu Glu Ser Ser Leu Glu Ser Asp Glu
115 120 125

Asp Glu Ser Glu Ser Glu Asp Glu Val Phe Asp Asp Ser Ile Cys Pro
130 135 140

Thr Asn Cys Asp Val Ala Leu Phe Glu Leu Ala Leu His Leu Arg Glu
145 150 155 160

Lys Arg Leu Asp Ile Glu Glu Ala Leu Val Glu Glu Lys Lys Ile Val
165 170 175

Asp Asn Leu Lys Lys Glu Tyr Asp Thr Leu Ser Lys Lys Val Lys Ile
180 185 190

Val Ala Thr Asn Leu Asn Ala Ala Glu Glu Ala Leu Glu Ala Tyr Gln

195	200	205
Arg Glu Lys Gln Gln Arg Leu Asn Glu Leu Leu Val Val Ile Pro Leu 210 215 220		
Lys Leu His Gln Ile Glu Tyr Val Val Phe Gly Glu Ile Pro Ser Asp 225 230 235 240		
Leu Ser Gly Thr Leu Val Phe Ser Asn His Ala Leu Arg Arg Leu Gln 245 250 255		
Glu Arg Ile Arg Glu Leu Gln Glu Glu Asn Ser Lys Gln Gln Lys Leu 260 265 270		
Asn Lys Glu Trp Arg Glu Arg Arg Lys Gln Leu Ile Arg Glu Lys Arg 275 280 285		
Glu Met Thr Lys Thr Ile His Lys Met Glu Glu Thr Val Arg Gln Leu 290 295 300		
Met Ile Ser Lys Phe Gly Arg Val Val Asn Leu Glu Ala Leu Gln Thr 305 310 315 320		
Leu Ser Val Asn Thr Thr Leu Glu Glu Leu Lys Ile Arg Lys Leu Arg 325 330 335		
Lys Glu Leu Ala Asn Ala Lys Glu Met Lys Met Trp Glu Glu Lys Ile 340 345 350		
Ala Gln Met Arg Trp Glu Leu Met Met Lys Thr Lys Glu His Thr Arg 355 360 365		
Lys Leu Tyr Gln Met Asn Asp Leu Cys Ile Glu Lys Lys Lys Leu Asp 370 375 380		
Ser Arg Leu Asn Thr Leu Gln Asn Gln Gln Asn Pro Gly Asn Gly Leu 385 390 395 400		

Ser

<210> 109
 <211> 1674
 <212> PRT
 <213> Homo sapiens

<400> 109

Met Glu Asp Ala Ser Glu Ser Ser Arg Gly Val Ala Pro Leu Ile Asn
 1 5 10 15
 Asn Val Val Leu Pro Gly Ser Pro Leu Ser Leu Pro Val Ser Val Thr
 20 25 30
 Gly Cys Lys Ser His Arg Val Ala Asn Lys Lys Val Glu Ala Arg Ser
 35 40 45
 Glu Lys Leu Leu Pro Thr Ala Leu Pro Pro Ser Glu Pro Lys Val Asp
 50 55 60
 Gln Lys Leu Pro Arg Ser Ser Glu Arg Arg Gly Ser Gly Gly Gly Thr
 65 70 75 80
 Gln Phe Pro Ala Arg Ser Arg Ala Val Ala Ala Gly Glu Ala Ala Ala
 85 90 95
 Arg Gly Ala Ala Gly Pro Glu Arg Gly Ser Pro Leu Gly Arg Arg Val
 100 105 110
 Ser Pro Arg Cys Leu Cys Ser Gly Glu Gly Gly Gln Val Ala Val Gly
 115 120 125
 Val Ile Ala Gly Lys Arg Gly Arg Arg Gly Arg Asp Gly Ser Arg Arg
 130 135 140
 Ala Pro Gly Gly Arg Glu Met Pro Leu Leu His Arg Lys Pro Phe Val
 145 150 155 160
 Arg Gln Lys Pro Pro Ala Asp Leu Arg Pro Asp Glu Glu Val Phe Tyr
 165 170 175
 Cys Lys Val Thr Asn Glu Ile Phe Arg His Tyr Asp Asp Phe Phe Glu
 180 185 190
 Arg Thr Ile Leu Cys Asn Ser Leu Val Trp Ser Cys Ala Val Thr Gly
 195 200 205
 Arg Pro Gly Leu Thr Tyr Gln Glu Ala Leu Glu Ser Glu Lys Lys Ala
 210 215 220
 Arg Gln Asn Leu Gln Ser Phe Pro Glu Pro Leu Ile Ile Pro Val Leu
 225 230 235 240
 Tyr Leu Thr Ser Leu Thr His Arg Ser Arg Leu His Glu Ile Cys Asp
 245 250 255

Asp Ile Phe Ala Tyr Val Lys Asp Arg Tyr Phe Val Glu Glu Thr Val
 260 265 270
 Glu Val Ile Arg Asn Asn Gly Ala Arg Leu Gln Cys Thr Ile Leu Glu
 275 280 285
 Val Leu Pro Pro Ser His Gln Asn Gly Phe Ala Asn Gly His Val Asn
 290 295 300
 Ser Val Asp Gly Glu Thr Ile Ile Ile Ser Asp Ser Asp Asp Ser Glu
 305 310 315 320
 Thr Gln Ser Cys Ser Phe Gln Asn Gly Lys Lys Lys Asp Ala Ile Asp
 325 330 335
 Pro Leu Leu Phe Lys Tyr Lys Val Gln Pro Thr Lys Lys Glu Leu His
 340 345 350
 Glu Ser Ala Ile Val Lys Ala Thr Gln Ile Ser Arg Arg Lys His Leu
 355 360 365
 Phe Ser Arg Asp Lys Leu Lys Leu Phe Leu Lys Gln His Cys Glu Pro
 370 375 380
 Gln Glu Gly Val Ile Lys Ile Lys Ala Ser Ser Leu Ser Thr Tyr Lys
 385 390 395 400
 Ile Ala Glu Gln Asp Phe Ser Tyr Phe Phe Pro Asp Asp Pro Pro Thr
 405 410 415
 Phe Ile Phe Ser Pro Ala Asn Arg Arg Arg Gly Arg Pro Pro Lys Arg
 420 425 430
 Ile His Ile Ser Gln Glu Asp Asn Val Ala Asn Lys Gln Thr Leu Ala
 435 440 445
 Ser Tyr Arg Ser Lys Ala Thr Lys Glu Arg Asp Lys Leu Leu Lys Gln
 450 455 460
 Glu Glu Met Lys Ser Leu Ala Phe Glu Lys Ala Lys Leu Lys Arg Glu
 465 470 475 480
 Lys Ala Asp Ala Leu Glu Ala Lys Lys Lys Glu Lys Glu Asp Lys Glu
 485 490 495

Lys Lys Arg Glu Glu Leu Lys Lys Ile Val Glu Glu Glu Arg Leu Lys
 500 505 510

Lys Lys Glu Glu Lys Glu Arg Leu Lys Val Glu Arg Glu Lys Glu Arg
 515 520 525

Glu Lys Leu Arg Glu Glu Lys Arg Lys Tyr Val Glu Tyr Leu Lys Gln
 530 535 540

Trp Ser Lys Pro Arg Glu Asp Met Glu Cys Asp Asp Leu Lys Glu Leu
 545 550 555 560

Pro Glu Pro Thr Pro Val Lys Thr Arg Leu Pro Pro Glu Ile Phe Gly
 565 570 575

Asp Ala Leu Met Val Leu Glu Phe Leu Asn Ala Phe Gly Glu Leu Phe
 580 585 590

Asp Leu Gln Asp Glu Phe Pro Asp Gly Val Thr Leu Glu Val Leu Glu
 595 600 605

Glu Ala Leu Val Gly Asn Asp Ser Glu Gly Pro Leu Cys Glu Leu Leu
 610 615 620

Phe Phe Phe Leu Thr Ala Ile Phe Gln Ala Ile Ala Glu Glu Glu Glu
 625 630 635 640

Glu Val Ala Lys Glu Gln Leu Thr Asp Ala Asp Thr Lys Gly Cys Ser
 645 650 655

Leu Lys Ser Leu Asp Leu Asp Ser Cys Thr Leu Ser Glu Ile Leu Arg
 660 665 670

Leu His Ile Leu Ala Ser Gly Ala Asp Val Thr Ser Ala Asn Ala Lys
 675 680 685

Tyr Arg Tyr Gln Lys Arg Gly Gly Phe Asp Ala Thr Asp Asp Ala Cys
 690 695 700

Met Glu Leu Arg Leu Ser Asn Pro Ser Leu Val Lys Lys Leu Ser Ser
 705 710 715 720

Thr Ser Val Tyr Asp Leu Thr Pro Gly Glu Lys Met Lys Ile Leu His
 725 730 735

Ala Leu Cys Gly Lys Leu Leu Thr Leu Val Ser Thr Arg Asp Phe Ile
 740 745 750

Glu Asp Tyr Val Asp Ile Leu Arg Gln Ala Lys Gln Glu Phe Arg Glu
 755 760 765
 Leu Lys Ala Glu Gln His Arg Lys Glu Arg Glu Glu Ala Ala Ala Arg
 770 775 780
 Ile Arg Lys Arg Lys Glu Glu Lys Leu Lys Glu Gln Glu Gln Lys Met
 785 790 795 800
 Lys Glu Lys Gln Glu Lys Leu Lys Glu Asp Glu Gln Arg Asn Ser Thr
 805 810 815
 Ala Asp Ile Ser Ile Gly Glu Glu Glu Arg Glu Asp Phe Asp Thr Ser
 820 825 830
 Ile Glu Ser Lys Asp Thr Glu Gln Lys Glu Leu Asp Gln Asp Met Phe
 835 840 845
 Thr Glu Asp Glu Asp Asp Pro Gly Ser His Lys Arg Gly Arg Arg Gly
 850 855 860
 Lys Arg Gly Gln Asn Gly Phe Lys Glu Phe Thr Arg Gln Glu Gln Ile
 865 870 875 880
 Asn Cys Val Thr Arg Glu Leu Leu Thr Ala Asp Glu Glu Glu Ala Leu
 885 890 895
 Lys Gln Glu His Gln Arg Lys Glu Lys Glu Leu Leu Glu Lys Ile Gln
 900 905 910
 Ser Ala Ile Ala Cys Thr Asn Ile Phe Pro Leu Gly Arg Asp Arg Met
 915 920 925
 Tyr Arg Arg Tyr Trp Ile Phe Pro Ser Ile Pro Gly Leu Phe Ile Glu
 930 935 940
 Glu Asp Tyr Ser Gly Leu Thr Glu Asp Met Leu Leu Pro Arg Pro Ser
 945 950 955 960
 Ser Phe Gln Asn Asn Val Gln Ser Gln Asp Pro Gln Val Ser Thr Lys
 965 970 975
 Thr Gly Glu Pro Leu Met Ser Glu Ser Thr Ser Asn Ile Asp Gln Gly
 980 985 990

Pro	Arg	Asp	His	Ser	Val	Gln	Leu	Pro	Lys	Pro	Val	His	Lys	Pro	Asn
		995					1000						1005		
Arg	Trp	Cys	Phe	Tyr	Ser	Ser	Cys	Glu	Gln	Leu	Asp	Gln	Leu	Ile	
	1010					1015					1020				
Glu	Ala	Leu	Asn	Ser	Arg	Gly	His	Arg	Glu	Ser	Ala	Leu	Lys	Glu	
	1025					1030					1035				
Thr	Leu	Leu	Gln	Glu	Lys	Ser	Arg	Ile	Cys	Ala	Gln	Leu	Ala	Arg	
	1040					1045					1050				
Phe	Ser	Glu	Glu	Lys	Phe	His	Phe	Ser	Asp	Lys	Pro	Gln	Pro	Asp	
	1055					1060					1065				
Ser	Lys	Pro	Thr	Tyr	Ser	Arg	Gly	Arg	Ser	Ser	Asn	Ala	Tyr	Asp	
	1070					1075					1080				
Pro	Ser	Gln	Met	Cys	Ala	Glu	Lys	Gln	Leu	Glu	Leu	Arg	Leu	Arg	
	1085					1090					1095				
Asp	Phe	Leu	Leu	Asp	Ile	Glu	Asp	Arg	Ile	Tyr	Gln	Gly	Thr	Leu	
	1100					1105					1110				
Gly	Ala	Ile	Lys	Val	Thr	Asp	Arg	His	Ile	Trp	Arg	Ser	Ala	Leu	
	1115					1120					1125				
Glu	Ser	Gly	Arg	Tyr	Glu	Leu	Leu	Ser	Glu	Glu	Asn	Lys	Glu	Asn	
	1130					1135					1140				
Gly	Ile	Ile	Lys	Thr	Val	Asn	Glu	Asp	Val	Glu	Glu	Met	Glu	Ile	
	1145					1150					1155				
Asp	Glu	Gln	Thr	Lys	Val	Ile	Val	Lys	Asp	Arg	Leu	Leu	Gly	Ile	
	1160					1165					1170				
Lys	Thr	Glu	Thr	Pro	Ser	Thr	Val	Ser	Thr	Asn	Ala	Ser	Thr	Pro	
	1175					1180					1185				
Gln	Ser	Val	Ser	Ser	Val	Val	His	Tyr	Leu	Ala	Met	Ala	Leu	Phe	
	1190					1195					1200				
Gln	Ile	Glu	Gln	Gly	Ile	Glu	Arg	Arg	Phe	Leu	Lys	Ala	Pro	Leu	
	1205					1210					1215				
Asp	Ala	Ser	Asp	Ser	Gly	Arg	Ser	Tyr	Lys	Thr	Val	Leu	Asp	Arg	
	1220					1225					1230				

Trp Arg	Glu Ser Leu Leu Ser	Ser Ala Ser Leu Ser	Gln Val Phe
1235	1240	1245	
Leu His	Leu Ser Thr Leu Asp	Arg Ser Val Ile Trp	Ser Lys Ser
1250	1255	1260	
Ile Leu	Asn Ala Arg Cys Lys	Ile Cys Arg Lys Lys	Gly Asp Ala
1265	1270	1275	
Glu Asn	Met Val Leu Cys Asp	Gly Cys Asp Arg Gly	His His Thr
1280	1285	1290	
Tyr Cys	Val Arg Pro Lys Leu	Lys Thr Val Pro Glu	Gly Asp Trp
1295	1300	1305	
Phe Cys	Pro Glu Cys Arg Pro	Lys Gln Arg Cys Arg	Arg Leu Ser
1310	1315	1320	
Phe Arg	Gln Arg Pro Ser Leu	Glu Ser Asp Glu Asp	Val Glu Asp
1325	1330	1335	
Ser Met	Gly Gly Glu Asp Asp	Glu Val Asp Gly Asp	Glu Glu Glu
1340	1345	1350	
Gly Gln	Ser Glu Glu Glu Glu	Tyr Glu Val Glu Gln	Asp Glu Asp
1355	1360	1365	
Asp Ser	Gln Glu Glu Glu Glu	Val Ser Leu Pro Lys	Arg Gly Arg
1370	1375	1380	
Pro Gln	Val Arg Leu Pro Val	Lys Thr Arg Gly Lys	Leu Ser Ser
1385	1390	1395	
Ser Phe	Ser Ser Arg Gly Gln	Gln Gln Glu Pro Gly	Arg Tyr Pro
1400	1405	1410	
Ser Arg	Ser Gln Gln Ser Thr	Pro Lys Thr Thr Val	Ser Ser Lys
1415	1420	1425	
Thr Gly	Arg Ser Leu Arg Lys	Ile Asn Ser Ala Pro	Pro Thr Glu
1430	1435	1440	
Thr Lys	Ser Leu Arg Ile Ala	Ser Arg Ser Thr Arg	His Ser His
1445	1450	1455	

Gly Pro Leu Gln Ala Asp Val Phe Val Glu Leu Leu Ser Pro Arg
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Arg Lys Arg Arg Gly Arg Lys Ser Ala Asn Asn Thr Pro Glu Asn
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1595 1600 1605

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Arg Leu Gln Ala Phe Phe His Ile Gln Ala Gln Lys Leu Gly Leu
1640 1645 1650

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<212> PRT

<213> Homo sapiens

<400> 110

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Glu Thr Val Val Lys Glu Asp Glu Gly Arg Arg Glu Ser Ile Asn Asp
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Arg Ala Arg Arg Ser Pro Arg Lys Leu Pro Thr Ser Leu Lys Lys Gly
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Glu Arg Lys Trp Ala Pro Pro Lys Phe Leu Pro His Lys Tyr Asp Val
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Trp Cys His Val His Leu Lys Lys Ser Leu Ser Gly Ser Pro Leu Lys						
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Val Ala Leu Pro Ile Val Ala Ile Glu Asn Ile Leu Ser Phe Met Ser
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Tyr Asp Glu Ile Ser Gln Leu Arg Leu Val Cys Lys Arg Met Asp Leu
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355

360

365

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
9 October 2003 (09.10.2003)

PCT

(10) International Publication Number
WO 2003/083047 A3

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- (21) International Application Number: **PCT/US2003/006025** (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 28 February 2003 (28.02.2003)
- (25) Filing Language: English
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- (71) Applicant (*for all designated States except US*): **EX-ELIXIS, INC.** [US/US]; P.O. Box 511, 170 Harbor Way, South San Francisco, CA 94083-0511 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **BELVIN, Marcia** [US/US]; 921 Santa Fe Avenue, Albany, CA 94706 (US). **FRANCIS-LANG, Helen** [GB/US]; 1782 Pacific Avenue #2, San Francisco, CA 94109 (US). **FRIEDMAN, Lori** [US/US]; 113 Arundel Road, San Carlos, CA 94070 (US). **PLOWMAN, Gregory, D.** [US/US]; 35 Winding Way, San Carlos, CA 94070 (US). **HEUER, Timothy, S.** [US/US]; 581A Paloma Avenue, Pacifica, CA 94044 (US). **LI, Danxi** [CN/US]; 90 Behr Avenue, #302, San Francisco, CA 94131 (US). **FUNKE, Roel, P.** [NL/US]; 668 Sierra Point Road, Brisbane, CA 95005 (US).
- Published:
- with international search report
 - before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report: 19 August 2004
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 2003/083047 A3

(54) Title: **MP53s AS MODIFIERS OF THE p53 PATHWAY AND METHODS OF USE**

(57) Abstract: Human MP53 genes are identified as modulators of the p53 pathway, and thus are therapeutic targets for disorders associated with defective p53 function. Methods for identifying modulators of p53, comprising screening for agents that modulate the activity of MP53 are provided.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/06025

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : G01N 33/53; C12P 21/06

US CL : 435/7.2, 69.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/7.2, 69.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WANG, X. et al. Poly(ADP-ribosyl)ation is required for p53-dependent signal transduction induced by radiation. Oncogene, 1998, Vol. 17, pages 2819-2825, especially page 2820, and 2824.	1-7, 16-18
Y	US 5,804,396 A (PLOWMAN) 08 September 1998 (8.9.1998) entire document, especially column 7, lines 60-67, column 8, lines 1-60	1-7, 16-18
Y	US 5,885,961 A (SHOYAB et al) 23 March 1999 (23.3.1999) entire document.	1-7, 16-18
Y	OLLMANN, M. Drosophila p53 is a structural and functional homolog of the tumor suppressor p53. Cell, March 31, 2000, Vol. 101, pages 91-101.	1-7, 16-18

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

26 September 2003 (26.09.2003)

Date of mailing of the international search report

16 JUL 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

Suryaprabha Chunduru

Telephone No. 703-308-0196

Janice Ford
for

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/06025

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-7, and 16-18

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/06025

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-7, 16-18, drawn to a method of identifying a candidate p53 pathway modulating agent comprising a MP53 polypeptide.

Group II, claim(s) 1, 8-10, 16-19, drawn to a method of identifying a candidate p53 pathway modulating agent comprising a MP53 nucleic acid.

Group III, claim(s) 11-12, 21, drawn to a method for administering the candidate p53 pathway modulating agent into a model system detecting a phenotypic change in the system.

Group I Group IV, claim(s) 13-15, 20, 22, drawn to a method for modulating a p53 pathway of a cell comprising a MP53 polypeptide.

Group V, claim(s) 23-25, drawn to a method for diagnosing a disease in a patient.

The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The method of identifying a candidate p53 pathway modulating agent requiring a MP53 polypeptide in Group I and other methods claims in Groups II-V, do not share same special technical feature because each of the methods of Groups I-V are independent to each other and do not link to other methods and hence lack special technical feature that binds all the groups together.

Continuation of B. FIELDS SEARCHED Item 3:

Medline, Biosis, Embase, Lifesci, Caplus, EAST databases
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(54) Title: MEMBRANE ASSOCIATED PROTEINS

(57) Abstract: The invention provides human membrane associated proteins (MEMAP) and polynucleotides which identify and encode MEMAP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of MEMAP.

MEMBRANE ASSOCIATED PROTEINS

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of membrane associated
5 proteins and to the use of these sequences in the diagnosis, treatment, and prevention of cell
proliferative, autoimmune/inflammatory, neurological and gastrointestinal disorders.

BACKGROUND OF THE INVENTION

Eukaryotic cells are surrounded by plasma membranes which enclose the cell and maintain
10 an environment inside the cell that is distinct from its surroundings. In addition, eukaryotic
organisms are distinct from prokaryotes in possessing many intracellular organelle and vesicle
structures. Many of the metabolic reactions which distinguish eukaryotic biochemistry from
prokaryotic biochemistry take place within these structures. The plasma membrane and the
membranes surrounding organelles and vesicles are composed of phosphoglycerides, fatty acids,
15 cholesterol, phospholipids, glycolipids, proteoglycans, and proteins. These components confer
identity and functionality to the membranes with which they associate.

Integral Membrane Proteins

The majority of known integral membrane proteins are transmembrane proteins (TM) which
20 are characterized by an extracellular, a transmembrane, and an intracellular domain. TM domains are
typically comprised of 15 to 25 hydrophobic amino acids which are predicted to adopt an α -helical
conformation. TM proteins are classified as bitopic (Types I and II) and polytopic (Types III and IV)
(Singer, S.J. (1990) Annu. Rev. Cell Biol. 6:247-96). Bitopic proteins span the membrane once while
polytopic proteins contain multiple membrane-spanning segments. TM proteins that act as cell-
25 surface receptor proteins involved in signal transduction include growth and differentiation factor
receptors, and receptor-interacting proteins such as *Drosophila* pecanex and frizzled proteins, LIV-1
protein, NF2 protein, and GNS1/SUR4 eukaryotic integral membrane proteins. TM proteins also act
as transporters of ions or metabolites, such as gap junction channels (connexins) and ion channels,
and as cell anchoring proteins, such as lectins, integrins, and fibronectins. TM proteins act as vesicle
30 organelle-forming molecules, such as calveolins, or as cell recognition molecules, such as cluster of
differentiation (CD) antigens, glycoproteins, and mucins.

Many membrane proteins (MPs) contain amino acid sequence motifs that target these
proteins to specific subcellular sites. Examples of these motifs include PDZ domains, KDEL, RGD,
NGR, and GSL sequence motifs, von Willebrand factor A (vWFA) domains, and EGF-like domains.
35 RGD, NGR, and GSL motif-containing peptides have been used as drug delivery agents in cancer

treatments which target tumor vasculature (Arap, W. et al. (1998) Science, 279:377-380).

Furthermore, MPs may also contain amino acid sequence motifs, such as the carbohydrate recognition domain (CRD), also known as the C-type lectin domain, that mediate interactions with extracellular or intracellular molecules.

5 Membrane proteins may also interact with and regulate the properties of the membrane lipids. Phospholipid scramblase, a type II plasma membrane protein, mediates calcium dependent movement of phospholipids (PL) between membrane leaflets. Calcium induced remodeling of plasma membrane PL plays a key role in expression of platelet anticoagulant activity and in clearance of injured or apoptotic cells (Zhou Q. et al. (1997) J. Biol. Chem. 272:18240-18244). Scott syndrome, a
10 bleeding disorder, is caused by an inherited deficiency in plasma membrane PL scramblase function (Online Mendelian Inheritance in Man (OMIM) *262890 Platelet Receptor for Factor X, Deficiency of).

Chemical modification of amino acid residue side chains alters the manner in which MPs interact with other molecules, such as phospholipid membranes. Examples of such chemical
15 modifications to amino acid residue side chains are covalent bond formation with glycosaminoglycans, oligosaccharides, phospholipids, acetyl and palmitoyl moieties, ADP-ribose, phosphate, and sulphate groups.

One function of TM proteins is to facilitate cell-cell communication. The slit proteins are extracellular matrix proteins expressed by cells at the ventral midline of the nervous system. Slit
20 proteins are ligands for the repulsive guidance receptor Robo and thus play a role in repulsive axon guidance (Brose, K. et al. (1999) Cell 96:795-806).

In some cases TM proteins serve as transporters or channels in the cell membrane. For example, the mouse transporter protein (MTP) has four transmembrane domains and resides in an intracellular membrane compartment. MTP can mediate transport of nucleosides in vitro. The role
25 of MTP in the cell may therefore be to transfer nucleosides between the cytosol and the lumen of intracellular organelles (Hogue, D. L. (1996) J. Biol. Chem. 271:9801-9808). The human stomatin-like protein (hSLP-1), expressed primarily in the brain, contains an N-terminal domain similar to the erythrocyte internal membrane protein stomatin, as well as a non-specific lipid transfer protein domain at the C-terminus. hSLP-1 is the human homologue of the C. elegans behavioral gene unc-
30 24, which is believed to be involved in lipid transfer between closely apposed membranes (Seidel, G. and Prohaska, R (1998) Gene 225:23-29).

The transmembrane 4 superfamily (TM4SF) or tetraspan family is a multigene family encoding type III integral membrane proteins (Wright, M.D. and Tomlinson, M.G. (1994) Immunol. Today 15:588-594). TM4SF is comprised of membrane proteins which traverse the cell membrane
35 four times. Members of the TM4SF include platelet and endothelial cell membrane proteins,

melanoma-associated antigens, leukocyte surface glycoproteins, colonal carcinoma antigens, tumor-associated antigens, and surface proteins of the schistosome parasites (Jankowski, S.A. (1994) Oncogene 9:1205-1211). Members of the TM4SF share about 25-30% amino acid sequence identity with one another.

5 A number of TM4SF members have been implicated in signal transduction, control of cell adhesion, regulation of cell growth and proliferation, including development and oncogenesis, and cell motility, including tumor cell metastasis. Expression of TM4SF proteins is associated with a variety of tumors and the level of expression may be altered when cells are growing or activated.

Tumor antigens are cell surface molecules that are differentially expressed in tumor cells
10 relative to normal cells. Tumor antigens distinguish tumor cells immunologically from normal cells and provide diagnostic and therapeutic targets for human cancers (Takagi, S. et al. (1995) Int. J. Cancer 61: 706-715; Liu, E. et al. (1992) Oncogene 7: 1027-1032). For example, the biliary glycoprotein-encoding gene is a member of the human carcinoembryonic antigen family, which are important tumor markers for colorectal carcinomas (Hammarstrom, S. (1999) Semin. Cancer Bio.
15 9:67-81). Another example is the neuron and testis specific protein Ma1, a marker for paraneoplastic neuronal disorders (Dalmau, J. et al. (1999) Brain 122:27-39).

Other types of cell surface antigens include those identified on leukocytic cells of the immune system. These antigens have been identified using systematic, monoclonal antibody (mAb)-based "shot gun" techniques. These techniques have resulted in the production of hundreds of mAbs
20 directed against unknown cell surface leukocytic antigens. These antigens have been grouped into "clusters of differentiation" based on common immunocytochemical localization patterns in various differentiated and undifferentiated leukocytic cell types. Antigens in a given cluster are presumed to identify a single cell surface protein and are assigned a "cluster of differentiation" or "CD" designation. Some of the genes encoding proteins identified by CD antigens have been cloned and
25 verified by standard molecular biology techniques. CD antigens have been characterized as both transmembrane proteins and cell surface proteins anchored to the plasma membrane via covalent attachment to fatty acid-containing glycolipids such as glycosylphosphatidylinositol (GPI). (Reviewed in Barclay, A. N. et al. (1995) The Leucocyte Antigen Facts Book, Academic Press, San Diego, CA, pp. 17-20.)

30 The TM cell surface glycoprotein CD69 is an early activation antigen of T lymphocytes. CD69 is homologous to members of a supergene family of type II integral membrane proteins having C-type lectin domains. Although the precise functions of the CD-69 antigen is not known, evidence suggests that these proteins transmit mitogenic signals across the plasma membrane and are up-regulated in response to lymphocyte activation (Hamann, J. et. al. (1993) J. Immunol. 150:4920-
35 4927).

Macrophages are involved in functions including clearance of senescent or apoptotic cells, cytokine production, hemopoiesis, bone resorption, antigen transport, and neuroendocrine regulation. These diverse roles are influenced by specialized macrophage plasma membrane proteins. The murine macrophage restricted C-type lectin is a type II integral membrane protein expressed
5 exclusively in macrophages. The strong expression of this protein in bone marrow suggests a hemopoietic function, while the lectin domain suggests it may be involved in cell-cell recognition (Balch, S. G. et al. (1998) *J. Biol. Chem.* 273:18656-18664).

The surface of red blood cells is populated with characteristic glycoproteins, such as the major sialoglycoproteins glycophorin A and B. Red blood cells lacking either glycophorin A or B are
10 resistant to infection with the malaria parasite *Plasmodium falciparum* (OMIM Entry 111300 Blood Group-MN Locus). White blood cells also possess characteristic surface glycoproteins, such as the plasma cell glycoprotein-1 (PC-1). PC-1 is expressed on the surface of plasma cells, which are terminally differentiated, antibody-secreting B-lymphocytes. The extracellular domain of PC-1 has nucleotide phosphodiesterase (pyrophosphatase) activity (Funakoshi, I. et al. (1992) *Arch. Biochem.*
15 *Biophys.* 295:180-187). Phosphodiesterase activity is associated with the hydrolytic removal of nucleotide subunits from oligonucleotides. Although the precise physiological role of PC-1 is not clear, increased PC-1 phosphodiesterase activity has been correlated with insulin resistance in patients with noninsulin-dependent diabetes mellitus, with abnormalities of bone mineralization and calcification, and with defects in renal tubule function. In addition, it appears that hPC-1 and mPC-1
20 are members of a multigene family of transmembrane phosphodiesterases with extracellular active sites. These enzymes may play a role in regulating the concentration of pharmacologically active extracellular compounds such as adenosine or other nucleotide derivatives in a variety of tissues and cell types. (Reviewed in Goding, J. W. et al. (1998) *Immunol. Rev.* 161:11-26.)

25 Peripheral and Anchored Membrane Proteins

Some membrane proteins are not membrane-spanning but are attached to the plasma membrane via membrane anchors or interactions with integral membrane proteins. Membrane anchors are covalently joined to a protein post-translationally and include such moieties as prenyl, myristyl, and glycosylphosphatidyl inositol (GPI) groups. Membrane localization of peripheral and
30 anchored proteins is important for their function in processes such as receptor-mediated signal transduction. For example, prenylation of Ras is required for its localization to the plasma membrane and for its normal and oncogenic functions in signal transduction.

The pancortins are a group of four glycoproteins which are predominantly expressed in the cerebral cortex of adult rodents. Immunological localization indicates that the pancortins are
35 endoplasmic reticulum anchored proteins. The pancortins share a common sequence in the middle of

their structure, but have alternative sequences at both ends due to differential promoter usage and alternative splicing. Each pancortin appears to be differentially expressed and may perform different functions in the brain (Nagano, T. et al. (1998) Mol. Brain Res. 53:13-23).

The discovery of new membrane associated proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of cell proliferative, autoimmune/inflammatory, neurological and gastrointestinal disorders.

SUMMARY OF THE INVENTION

The invention features purified polypeptides, membrane associated proteins, referred to collectively as "MEMAP" and individually as "MEMAP-1," "MEMAP-2," "MEMAP-3," "MEMAP-4," "MEMAP-5," "MEMAP-6," "MEMAP-7," "MEMAP-8," "MEMAP-9," "MEMAP-10," "MEMAP-11," "MEMAP-12," "MEMAP-13," "MEMAP-14," "MEMAP-15," "MEMAP-16," "MEMAP-17," "MEMAP-18," "MEMAP-19," "MEMAP-20," "MEMAP-21," "MEMAP-22," "MEMAP-23," "MEMAP-24," "MEMAP-25," "MEMAP-26," "MEMAP-27," "MEMAP-28," "MEMAP-29," "MEMAP-30," "MEMAP-31," "MEMAP-32," "MEMAP-33," "MEMAP-34," "MEMAP-35," "MEMAP-36," and "MEMAP-37." In one aspect, the invention provides an isolated polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37. In one alternative, the invention provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-37.

The invention further provides an isolated polynucleotide encoding a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37. In one alternative, the polynucleotide encodes a polypeptide selected from the group consisting of SEQ ID NO:1-37. In another alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:38-74.

Additionally, the invention provides a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding a polypeptide comprising an amino acid

sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, c) a biologically active fragment of an amino acid sequence selected from the group consisting of
5 SEQ ID NO:1-37, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37. In one alternative, the invention provides a cell transformed with the recombinant polynucleotide. In another alternative, the invention provides a transgenic organism comprising the recombinant polynucleotide.

The invention also provides a method for producing a polypeptide comprising an amino acid
10 sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, c) a biologically active fragment of an amino acid sequence selected from the group consisting of
15 SEQ ID NO:1-37, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the polypeptide, and b) recovering the polypeptide so expressed.

Additionally, the invention provides an isolated antibody which specifically binds to a
20 polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, and d) an immunogenic fragment of an amino
25 acid sequence selected from the group consisting of SEQ ID NO:1-37.

The invention further provides an isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74, b) a naturally occurring polynucleotide sequence having at least
30 70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). In one alternative, the polynucleotide comprises at least 60 contiguous nucleotides.

Additionally, the invention provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide
35 sequence selected from the group consisting of a) a polynucleotide sequence selected from the group

consisting of SEQ ID NO:38-74, b) a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and b) detecting the presence or absence of said hybridization complex, and optionally, if present, the amount thereof. In one alternative, the probe comprises at least 60 contiguous nucleotides.

The invention further provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74, b) a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74, c) a polynucleotide sequence complementary to a), d) a polynucleotide sequence complementary to b), and e) an RNA equivalent of a)-d). The method comprises a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

The invention further provides a composition comprising an effective amount of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, and a pharmaceutically acceptable excipient. In one embodiment, the composition comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-37. The invention additionally provides a method of treating a disease or condition associated with decreased expression of functional MEMAP, comprising administering to a patient in need of such treatment the composition.

The invention also provides a method for screening a compound for effectiveness as an agonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence

selected from the group consisting of SEQ ID NO:1-37, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting
5 agonist activity in the sample. In one alternative, the invention provides a composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with decreased expression of functional MEMAP, comprising administering to a patient in need of such treatment the composition.

10 Additionally, the invention provides a method for screening a compound for effectiveness as an antagonist of a polypeptide comprising an amino acid sequence selected from the group consisting of a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence
15 acid sequence selected from the group consisting of SEQ ID NO:1-37, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a composition comprising an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In
20 another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional MEMAP, comprising administering to a patient in need of such treatment the composition.

The invention further provides a method of screening for a compound that specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of a) an
25 amino acid sequence selected from the group consisting of SEQ ID NO:1-37, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37. The method comprises a)
30 combining the polypeptide with at least one test compound under suitable conditions, and b) detecting binding of the polypeptide to the test compound, thereby identifying a compound that specifically binds to the polypeptide.

The invention further provides a method of screening for a compound that modulates the activity of a polypeptide comprising an amino acid sequence selected from the group consisting of a)
35 an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, b) a naturally

occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37, and d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-37. The method comprises a) combining the polypeptide with at least one test compound under conditions permissive for the activity of the polypeptide, b) assessing the activity of the polypeptide in the presence of the test compound, and c) comparing the activity of the polypeptide in the presence of the test compound with the activity of the polypeptide in the absence of the test compound, wherein a change in the activity of the polypeptide in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence selected from the group consisting of SEQ ID NO:38-74, the method comprising a) exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

The invention further provides a method for assessing toxicity of a test compound, said method comprising a) treating a biological sample containing nucleic acids with the test compound; b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide comprising a polynucleotide sequence selected from the group consisting of i) a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74, ii) a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74, iii) a polynucleotide sequence complementary to i), iv) a polynucleotide sequence complementary to ii), and v) an RNA equivalent of i)-iv). Hybridization occurs under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74, ii) a naturally occurring polynucleotide sequence having at least 70% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:38-74, iii) a polynucleotide sequence complementary to i), iv) a polynucleotide sequence complementary to ii), and v) an RNA equivalent of i)-iv). Alternatively, the target polynucleotide comprises a fragment of the above polynucleotide sequence; c) quantifying the amount of hybridization complex; and d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

BRIEF DESCRIPTION OF THE TABLES

Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID NOs), clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding MEMAP.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms, and searchable databases used for analysis of MEMAP.

Table 3 shows selected fragments of each nucleic acid sequence; the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis; diseases, disorders, or conditions associated with these tissues; and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding MEMAP were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze the polynucleotides and polypeptides of the invention, along with applicable descriptions, references, and threshold parameters.

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the

invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

“MEMAP” refers to the amino acid sequences of substantially purified MEMAP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term “agonist” refers to a molecule which intensifies or mimics the biological activity of MEMAP. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of MEMAP either by directly interacting with MEMAP or by acting on components of the biological pathway in which MEMAP participates.

An “allelic variant” is an alternative form of the gene encoding MEMAP. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

“Altered” nucleic acid sequences encoding MEMAP include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as MEMAP or a polypeptide with at least one functional characteristic of MEMAP. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding MEMAP, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding MEMAP. The encoded protein may also be “altered,” and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent MEMAP. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of MEMAP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms “amino acid” and “amino acid sequence” refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where “amino acid sequence” is recited to refer to a sequence of a naturally occurring

protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of MEMAP. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of MEMAP either by directly interacting with MEMAP or by acting on components of the biological pathway in which MEMAP participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')₂, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind MEMAP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition capable of base-pairing with the "sense" (coding) strand of a specific nucleic acid sequence. Antisense compositions may include DNA; RNA; peptide nucleic acid (PNA); oligonucleotides having modified backbone linkages such as phosphorothioates, methylphosphonates, or benzylphosphonates; oligonucleotides having modified sugar groups such as 2'-methoxyethyl sugars or 2'-methoxyethoxy sugars; or oligonucleotides having modified bases such as 5-methyl cytosine, 2'-deoxyuracil, or 7-deaza-2'-deoxyguanosine. Antisense molecules may be produced by any method including chemical synthesis or transcription. Once introduced into a cell, the complementary antisense molecule base-pairs with a naturally occurring nucleic acid sequence produced by the cell to form duplexes which block either transcription or translation. The designation "negative" or "minus" can refer to the antisense strand, and the

designation "positive" or "plus" can refer to the sense strand of a reference DNA molecule.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" or "immunogenic" refers to the capability of the natural, recombinant, or synthetic MEMAP, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

"Complementary" describes the relationship between two single-stranded nucleic acid sequences that anneal by base-pairing. For example, 5'-AGT-3' pairs with its complement, 3'-TCA-5'.

A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding MEMAP or fragments of MEMAP may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been subjected to repeated DNA sequence analysis to resolve uncalled bases, extended using the XL-PCR kit (PE Biosystems, Foster City CA) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from one or more overlapping cDNA, EST, or genomic DNA fragments using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI) or Phrap (University of Washington, Seattle WA). Some sequences have been both extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that are predicted to least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

30	Original Residue	Conservative Substitution
	Ala	Gly, Ser
	Arg	His, Lys
	Asn	Asp, Gln, His
	Asp	Asn, Glu
35	Cys	Ala, Ser
	Gln	Asn, Glu, His
	Glu	Asp, Gln, His

	Gly	Ala
	His	Asn, Arg, Gln, Glu
	Ile	Leu, Val
5	Leu	Ile, Val
	Lys	Arg, Gln, Glu
	Met	Leu, Ile
	Phe	His, Met, Leu, Trp, Tyr
	Ser	Cys, Thr
	Thr	Ser, Val
10	Trp	Phe, Tyr
	Tyr	His, Phe, Trp
	Val	Ile, Leu, Thr

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to a chemically modified polynucleotide or polypeptide. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "detectable label" refers to a reporter molecule or enzyme that is capable of generating a measurable signal and is covalently or noncovalently joined to a polynucleotide or polypeptide.

A "fragment" is a unique portion of MEMAP or the polynucleotide encoding MEMAP which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 16, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50% of a polypeptide) as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the

present embodiments.

A fragment of SEQ ID NO:38-74 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:38-74, for example, as distinct from any other sequence in the genome from which the fragment was obtained. A fragment of SEQ ID NO:38-74 is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:38-74 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:38-74 and the region of SEQ ID NO:38-74 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-37 is encoded by a fragment of SEQ ID NO:38-74. A fragment of SEQ ID NO:1-37 comprises a region of unique amino acid sequence that specifically identifies SEQ ID NO:1-37. For example, a fragment of SEQ ID NO:1-37 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-37. The precise length of a fragment of SEQ ID NO:1-37 and the region of SEQ ID NO:1-37 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A "full-length" polynucleotide sequence is one containing at least a translation initiation codon (e.g., methionine) followed by an open reading frame and a translation termination codon. A "full-length" polynucleotide sequence encodes a "full-length" polypeptide sequence.

"Homology" refers to sequence similarity or, interchangeably, sequence identity, between two or more polynucleotide sequences or two or more polypeptide sequences.

The terms "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequences.

Alternatively, a suite of commonly used and freely available sequence comparison algorithms

is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at <http://www.ncbi.nlm.nih.gov/BLAST/>. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at <http://www.ncbi.nlm.nih.gov/gorf/bl2.html>. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Reward for match: 1

15 *Penalty for mismatch: -2*

Open Gap: 5 and Extension Gap: 2 penalties

Gap x drop-off: 50

Expect: 10.

Word Size: 11

20 *Filter: on*

Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative

substitutions, explained in more detail above, generally preserve the charge and hydrophobicity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.12 (Apr-21-2000) with blastp set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Open Gap: 11 and Extension Gap: 1 penalties

Gap x drop-off: 50

Expect: 10

Word Size: 3

Filter: on

Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for chromosome replication, segregation and maintenance.

The term "humanized antibody" refers to an antibody molecule in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to the process by which a polynucleotide strand anneals with a complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of complementarity.

Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 µg/ml sheared, denatured salmon sperm DNA.

Generally, stringency of hybridization is expressed, in part, with reference to the temperature under which the wash step is carried out. Such wash temperatures are typically selected to be about 5°C to 20°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating T_m and conditions for nucleic acid hybridization are well known and can be found in Sambrook, J. et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, sheared and denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide

sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

“Immune response” can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

An “immunogenic fragment” is a polypeptide or oligopeptide fragment of MEMAP which is capable of eliciting an immune response when introduced into a living organism, for example, a mammal. The term “immunogenic fragment” also includes any polypeptide or oligopeptide fragment of MEMAP which is useful in any of the antibody production methods disclosed herein or known in the art.

The term “microarray” refers to an arrangement of a plurality of polynucleotides, polypeptides, or other chemical compounds on a substrate.

The terms “element” and “array element” refer to a polynucleotide, polypeptide, or other chemical compound having a unique and defined position on a microarray.

The term “modulate” refers to a change in the activity of MEMAP. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of MEMAP.

The phrases “nucleic acid” and “nucleic acid sequence” refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

“Operably linked” refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with a second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

“Peptide nucleic acid” (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

“Post-translational modification” of an MEMAP may involve lipidation, glycosylation, phosphorylation, acetylation, racemization, proteolytic cleavage, and other modifications known in the art. These processes may occur synthetically or biochemically. Biochemical modifications will vary by cell type depending on the enzymatic milieu of MEMAP.

"Probe" refers to nucleic acid sequences encoding MEMAP, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes.

- 5 "Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

Probes and primers as used in the present invention typically comprise at least 15 contiguous
10 nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

- 15 Methods for preparing and using probes and primers are described in the references, for example Sambrook, J. et al. (1989) Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel, F.M. et al. (1987) Current Protocols in Molecular Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis, M. et al. (1990) PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs
20 can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to
25 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from
30 megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection
35 programs may also be obtained from their respective sources and modified to meet the user's specific

needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both
5 unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

10 A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have
15 been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a
20 vaccinia virus, that could be used to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

A "regulatory element" refers to a nucleic acid sequence usually derived from untranslated regions of a gene and includes enhancers, promoters, introns, and 5' and 3' untranslated regions (UTRs). Regulatory elements interact with host or viral proteins which control transcription,
25 translation, or RNA stability.

"Reporter molecules" are chemical or biochemical moieties used for labeling a nucleic acid, amino acid, or antibody. Reporter molecules include radionuclides; enzymes; fluorescent, chemiluminescent, or chromogenic agents; substrates; cofactors; inhibitors; magnetic particles; and other moieties known in the art.

30 An "RNA equivalent," in reference to a DNA sequence, is composed of the same linear sequence of nucleotides as the reference DNA sequence with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic
35 acids encoding MEMAP, or fragments thereof, or MEMAP itself, may comprise a bodily fluid; an

extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide comprising the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least 60% free, preferably at least 75% free, and most preferably at least 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acid residues or nucleotides by different amino acid residues or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

A "transcript image" refers to the collective pattern of gene expression by a particular cell type or tissue under given conditions at a given time.

"Transformation" describes a process by which exogenous DNA is introduced into a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, bacteriophage or viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "transgenic organism," as used herein, is any organism, including but not limited to animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with

a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or in vitro fertilization, but rather is directed to the introduction of a recombinant DNA molecule. The transgenic organisms contemplated in accordance with the present invention include bacteria, cyanobacteria, fungi, plants, and animals. The isolated DNA of the present invention can be introduced into the host by methods known in the art, for example infection, transfection, transformation or transconjugation. Techniques for transferring the DNA of the present invention into such organisms are widely known and provided in references such as Sambrook, J. et al. (1989), supra.

A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternative splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

THE INVENTION

The invention is based on the discovery of new human membrane associated proteins (MEMAP), the polynucleotides encoding MEMAP, and the use of these compositions for the diagnosis, treatment, or prevention of cell proliferative, autoimmune/inflammatory, neurological and

gastrointestinal disorders.

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding MEMAP. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each MEMAP were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. In some cases, GenBank sequence identifiers are also shown in column 5. The Incyte clones and GenBank cDNA sequences, where indicated, in column 5 were used to assemble the consensus nucleotide sequence of each MEMAP and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows homologous sequences as identified by BLAST analysis; and column 7 shows analytical methods and in some cases, searchable databases to which the analytical methods were applied. The methods of column 7 were used to characterize each polypeptide through sequence homology and protein motifs:

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding MEMAP. The first column of Table 3 lists the nucleotide SEQ ID NOs. Column 2 lists fragments of the nucleotide sequences of column 1. These fragments are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:38-74 and to distinguish between SEQ ID NO:38-74 and related polynucleotide sequences. The polypeptides encoded by these fragments are useful, for example, as immunogenic peptides. Column 3 lists tissue categories which express MEMAP as a fraction of total tissues expressing MEMAP. Column 4 lists diseases, disorders, or conditions associated with those tissues expressing MEMAP as a fraction of total tissues expressing MEMAP. Column 5 lists the vectors used to subclone each cDNA library. Of particular note is the expression of SEQ ID NO:41, SEQ ID NO:48, and SEQ ID NO:56 in nervous tissues, of SEQ ID NO:52, SEQ ID NO:65, and SEQ ID NO:74 in gastrointestinal tissues, and of SEQ ID NO:55 in hematopoietic/immune tissues.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding MEMAP were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

SEQ ID NO:38 maps to chromosome 4 within the interval from 77.9 to 86.0 centiMorgans, to chromosome 6 within the interval from 132.7 to 144.4 centiMorgans, and to chromosome 14 within the interval from 89.4 to 103.7 centiMorgans. The interval on chromosome 4 from 77.9 to 86.0 centiMorgans also contains a gene associated with deoxycytidine kinase deficiency. The interval on chromosome 6 from 132.7 to 144.4 centiMorgans also contains genes associated with peroxisomal disorders and leukemia. The interval on chromosome 14 from 89.4 to 103.7 centiMorgans also contains genes associated with spinocerebellar ataxia and protease inhibitor deficiencies. SEQ ID NO:39 maps to chromosome 2 within the interval from 236.2 to 269.5 centiMorgans, and to the X chromosome within the interval from 94.4 to 97.4 centiMorgans. The interval on chromosome 2 from 236.2 to 269.5 centiMorgans also contains genes associated with Crigler-Najjar syndrome, Oguchi disease, and oxalosis I. The interval on the X chromosome from 94.4 to 97.4 centiMorgans also contains genes associated with Charcot-Marie tooth disease, X-linked severe combined immunodeficiency, alpha thalassemia/mental retardation syndrome, Menkes' syndrome, and choroideremia. SEQ ID NO:42 maps to chromosome 1 within the interval from 218.2 to 232.0 centiMorgans. This interval also contains genes associated with familial hypertrophic cardiomyopathy, malignant hyperthermia, and hypokalemic periodic paralysis. SEQ ID NO:44 maps to chromosome 7 within the interval from 136.4 to 145.8 centiMorgans, to chromosome 14 within the interval from 28.0 to 32.9 centiMorgans, and to chromosome 14 within the interval from 71.5 to 73.7 centiMorgans. The interval on chromosome 7 from 136.4 to 145.8 centiMorgans also contains genes associated with diphosphoglycerate mutase deficiency. SEQ ID NO:60 maps to chromosome 7 within the interval from 167.6 to 184.0 centiMorgans, and to chromosome 14 within the interval from 50.0 to 59.0 centiMorgans. SEQ ID NO:63 maps to chromosome 8 within the interval from 101.0 to 125.8 centiMorgans, and to chromosome 8 within the interval from 132.4 to 135.1 centiMorgans. SEQ ID NO:67 maps to chromosome 4 within the interval from 145.3 to 146.4 centiMorgans.

The invention also encompasses MEMAP variants. A preferred MEMAP variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the MEMAP amino acid sequence, and which contains at least one functional or structural characteristic of MEMAP.

The invention also encompasses polynucleotides which encode MEMAP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:38-74, which encodes MEMAP. The polynucleotide sequences of SEQ ID NO:38-74, as presented in the Sequence Listing, embrace the equivalent RNA sequences, wherein occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The invention also encompasses a variant of a polynucleotide sequence encoding MEMAP.

In particular, such a variant polynucleotide sequence will have at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding MEMAP. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID
5 NO:38-74 which has at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:38-74. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of MEMAP.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the
10 genetic code, a multitude of polynucleotide sequences encoding MEMAP, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the
15 polynucleotide sequence of naturally occurring MEMAP, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode MEMAP and its variants are generally capable of hybridizing to the nucleotide sequence of the naturally occurring MEMAP under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding
20 MEMAP or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding MEMAP and its derivatives without altering the encoded amino acid
25 sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode MEMAP and MEMAP derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell
30 systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding MEMAP or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:38-74 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and
35 S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol.

152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (PE Biosystems, Foster City CA), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (PE Biosystems). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (PE Biosystems), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding MEMAP may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-3060). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National

Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been
5 size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze
10 the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, PE Biosystems), and the entire
15 process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode MEMAP may be cloned in recombinant DNA molecules that direct expression of
20 MEMAP, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express MEMAP.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter MEMAP-encoding sequences for a variety of purposes including,
25 but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

30 The nucleotides of the present invention may be subjected to DNA shuffling techniques such as MOLECULARBREEDING (Maxygen Inc., Santa Clara CA; described in U.S. Patent Number 5,837,458; Chang, C.-C. et al. (1999) Nat. Biotechnol. 17:793-797; Christians, F.C. et al. (1999) Nat. Biotechnol. 17:259-264; and Crameri, A. et al. (1996) Nat. Biotechnol. 14:315-319) to alter or improve the biological properties of MEMAP, such as its biological or enzymatic activity or its
35 ability to bind to other molecules or compounds. DNA shuffling is a process by which a library of

gene variants is produced using PCR-mediated recombination of gene fragments. The library is then subjected to selection or screening procedures that identify those gene variants with the desired properties. These preferred variants may then be pooled and further subjected to recursive rounds of DNA shuffling and selection/screening. Thus, genetic diversity is created through "artificial" breeding and rapid molecular evolution. For example, fragments of a single gene containing random point mutations may be recombined, screened, and then reshuffled until the desired properties are optimized. Alternatively, fragments of a given gene may be recombined with fragments of homologous genes in the same gene family, either from the same or different species, thereby maximizing the genetic diversity of multiple naturally occurring genes in a directed and controllable manner.

In another embodiment, sequences encoding MEMAP may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al: (1980) *Nucleic Acids Symp. Ser. 7*:215-223; Horn, T. et al. (1980) *Nucleic Acids Symp. Ser. 7*:225-232.) Alternatively, MEMAP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solution-phase or solid-phase techniques. (See, e.g., Creighton, T. (1984) *Proteins, Structures and Molecular Properties*, WH Freeman, New York NY, pp. 55-60; and Roberge, J.Y. et al. (1995) *Science* 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (PE Biosystems). Additionally, the amino acid sequence of MEMAP, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide or a polypeptide having a sequence of a naturally occurring polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) *Methods Enzymol.* 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, *supra*, pp. 28-53.)

In order to express a biologically active MEMAP, the nucleotide sequences encoding MEMAP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding MEMAP. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding MEMAP. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding MEMAP and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no

additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic.

- 5 The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding MEMAP and appropriate transcriptional and translational
10 control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

- 15 A variety of expression vector/host systems may be utilized to contain and express sequences encoding MEMAP. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower
20 mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. (See, e.g., Sambrook, supra; Ausubel, supra; Van Heeke, G. and S.M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509; Bitter, G.A. et al. (1987) *Methods Enzymol.* 153:516-544; Scorer, C.A. et al. (1994) *Bio/Technology* 12:181-184; Engelhard, E.K. et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:3224-3227; Sandig, V. et al. (1996) *Hum. Gene Ther.* 7:1937-
25 1945; Takamatsu, N. (1987) *EMBO J.* 6:307-311; Coruzzi, G. et al. (1984) *EMBO J.* 3:1671-1680; Broglie, R. et al. (1984) *Science* 224:838-843; Winter, J. et al. (1991) *Results Probl. Cell Differ.* 17:85-105; The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196; Logan, J. and T. Shenk (1984) *Proc. Natl. Acad. Sci. USA* 81:3655-3659; and Harrington, J.J. et al. (1997) *Nat. Genet.* 15:345-355.) Expression vectors derived from retroviruses,
30 adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. (See, e.g., Di Nicola, M. et al. (1998) *Cancer Gen. Ther.* 5(6):350-356; Yu, M. et al. (1993) *Proc. Natl. Acad. Sci. USA* 90(13):6340-6344; Buller, R.M. et al. (1985) *Nature* 317(6040):813-815; McGregor, D.P. et al. (1994) *Mol. Immunol.* 31(3):219-226; and Verma, I.M. and N. Somia (1997) *Nature* 389:239-242.)
- 35 The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding MEMAP. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding MEMAP can be achieved using a multifunctional *E. coli* vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORT1
5 plasmid (Life Technologies). Ligation of sequences encoding MEMAP into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for *in vitro* transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol.
10 Chem. 264:5503-5509.) When large quantities of MEMAP are needed, e.g. for the production of antibodies, vectors which direct high level expression of MEMAP may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of MEMAP. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH
15 promoters, may be used in the yeast *Saccharomyces cerevisiae* or *Pichia pastoris*. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, *supra*; Bitter, *supra*; and Scorer, *supra*.)

Plant systems may also be used for expression of MEMAP. Transcription of sequences
20 encoding MEMAP may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, *supra*; Broglie, *supra*; and Winter, *supra*.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated
25 transfection. (See, e.g., *The McGraw Hill Yearbook of Science and Technology* (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding MEMAP may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite
30 leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses MEMAP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

35 Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of

DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

5 For long term production of recombinant proteins in mammalian systems, stable expression of MEMAP in cell lines is preferred. For example, sequences encoding MEMAP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in
10 enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These
15 include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk*⁻ and *apr*⁻ cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat*
20 confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins
25 (GFP; Clontech), β glucuronidase and its substrate β -glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is
30 also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding MEMAP is inserted within a marker gene sequence, transformed cells containing sequences encoding MEMAP can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding MEMAP under the control of a single promoter. Expression of the marker gene in response to induction or selection
35 usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding MEMAP and that express MEMAP may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of MEMAP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on MEMAP is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding MEMAP include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding MEMAP, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes *in vitro* by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding MEMAP may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode MEMAP may be designed to contain signal sequences which direct secretion of MEMAP through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of

the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity.

Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding MEMAP may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric MEMAP protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of MEMAP activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the MEMAP encoding sequence and the heterologous protein sequence, so that MEMAP may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, *supra*, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled MEMAP may be achieved *in vitro* using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, ³⁵S-methionine.

MEMAP of the present invention or fragments thereof may be used to screen for compounds that specifically bind to MEMAP. At least one and up to a plurality of test compounds may be screened for specific binding to MEMAP. Examples of test compounds include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

In one embodiment, the compound thus identified is closely related to the natural ligand of

MEMAP, e.g., a ligand or fragment thereof, a natural substrate, a structural or functional mimetic, or a natural binding partner. (See, Coligan, J.E. et al. (1991) Current Protocols in Immunology 1(2): Chapter 5.) Similarly, the compound can be closely related to the natural receptor to which MEMAP binds, or to at least a fragment of the receptor, e.g., the ligand binding site. In either case, the compound can be rationally designed using known techniques. In one embodiment, screening for these compounds involves producing appropriate cells which express MEMAP, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or E. coli. Cells expressing MEMAP or cell membrane fractions which contain MEMAP are then contacted with a test compound and binding, stimulation, or inhibition of activity of either MEMAP or the compound is analyzed.

An assay may simply test binding of a test compound to the polypeptide, wherein binding is detected by a fluorophore, radioisotope, enzyme conjugate, or other detectable label. For example, the assay may comprise the steps of combining at least one test compound with MEMAP, either in solution or affixed to a solid support, and detecting the binding of MEMAP to the compound. Alternatively, the assay may detect or measure binding of a test compound in the presence of a labeled competitor. Additionally, the assay may be carried out using cell-free preparations, chemical libraries, or natural product mixtures, and the test compound(s) may be free in solution or affixed to a solid support.

MEMAP of the present invention or fragments thereof may be used to screen for compounds that modulate the activity of MEMAP. Such compounds may include agonists, antagonists, or partial or inverse agonists. In one embodiment, an assay is performed under conditions permissive for MEMAP activity, wherein MEMAP is combined with at least one test compound, and the activity of MEMAP in the presence of a test compound is compared with the activity of MEMAP in the absence of the test compound. A change in the activity of MEMAP in the presence of the test compound is indicative of a compound that modulates the activity of MEMAP. Alternatively, a test compound is combined with an in vitro or cell-free system comprising MEMAP under conditions suitable for MEMAP activity, and the assay is performed. In either of these assays, a test compound which modulates the activity of MEMAP may do so indirectly and need not come in direct contact with the test compound. At least one and up to a plurality of test compounds may be screened.

In another embodiment, polynucleotides encoding MEMAP or their mammalian homologs may be "knocked out" in an animal model system using homologous recombination in embryonic stem (ES) cells. Such techniques are well known in the art and are useful for the generation of animal models of human disease. (See, e.g., U.S. Patent No. 5,175,383 and U.S. Patent No. 5,767,337.) For example, mouse ES cells, such as the mouse 129/SvJ cell line, are derived from the early mouse embryo and grown in culture. The ES cells are transformed with a vector containing the gene of

interest disrupted by a marker gene, e.g., the neomycin phosphotransferase gene (neo; Capecchi, M.R. (1989) Science 244:1288-1292). The vector integrates into the corresponding region of the host genome by homologous recombination. Alternatively, homologous recombination takes place using the Cre-loxP system to knockout a gene of interest in a tissue- or developmental stage-specific manner (Marth, J.D. (1996) Clin. Invest. 97:1999-2002; Wagner, K.U. et al. (1997) Nucleic Acids Res. 25:4323-4330). Transformed ES cells are identified and microinjected into mouse cell blastocysts such as those from the C57BL/6 mouse strain. The blastocysts are surgically transferred to pseudopregnant dams, and the resulting chimeric progeny are genotyped and bred to produce heterozygous or homozygous strains. Transgenic animals thus generated may be tested with potential therapeutic or toxic agents.

Polynucleotides encoding MEMAP may also be manipulated in vitro in ES cells derived from human blastocysts. Human ES cells have the potential to differentiate into at least eight separate cell lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate into, for example, neural cells, hematopoietic lineages, and cardiomyocytes (Thomson, J.A. et al. (1998) Science 282:1145-1147).

Polynucleotides encoding MEMAP can also be used to create "knockin" humanized animals (pigs) or transgenic animals (mice or rats) to model human disease. With knockin technology, a region of a polynucleotide encoding MEMAP is injected into animal ES cells, and the injected sequence integrates into the animal cell genome. Transformed cells are injected into blastulae, and the blastulae are implanted as described above. Transgenic progeny or inbred lines are studied and treated with potential pharmaceutical agents to obtain information on treatment of a human disease. Alternatively, a mammal inbred to overexpress MEMAP, e.g., by secreting MEMAP in its milk, may also serve as a convenient source of that protein (Janne, J. et al. (1998) Biotechnol. Annu. Rev. 4:55-74).

25 THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of MEMAP and membrane associated proteins. In addition, the expression of MEMAP is closely associated with neurological and gastrointestinal tissues, cancer, cell proliferation, and inflammation/trauma. Therefore, MEMAP appears to play a role in cell proliferative, autoimmune/inflammatory, neurological and gastrointestinal disorders. In the treatment of disorders associated with increased MEMAP expression or activity, it is desirable to decrease the expression or activity of MEMAP. In the treatment of disorders associated with decreased MEMAP expression or activity, it is desirable to increase the expression or activity of MEMAP.

Therefore, in one embodiment, MEMAP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or

activity of MEMAP. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma,

5 leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an autoimmune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory

10 distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis,

15 glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis,

20 Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural

25 muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-

30 Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic,

35 endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including

mood, anxiety, and schizophrenic disorders, seasonal affective disorder (SAD), akathisia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, Tourette's disorder, progressive supranuclear palsy, corticobasal degeneration, and familial frontotemporal dementia; and a gastrointestinal disorder such as dysphagia, peptic esophagitis, esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis, hyperbilirubinemia, cirrhosis, passive congestion of the liver, hepatoma, infectious colitis, ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, acquired immunodeficiency syndrome (AIDS) enteropathy, jaundice, hepatic encephalopathy, hepatorenal syndrome, hepatic steatosis, hemochromatosis, Wilson's disease, alpha₁-antitrypsin deficiency, Reye's syndrome, primary sclerosing cholangitis, liver infarction, portal vein obstruction and thrombosis, centrilobular necrosis, peliosis hepatis, hepatic vein thrombosis, veno-occlusive disease, preeclampsia, eclampsia, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and hepatic tumors including nodular hyperplasias, adenomas, and carcinomas.

In another embodiment, a vector capable of expressing MEMAP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of MEMAP including, but not limited to, those described above.

In a further embodiment, a composition comprising a substantially purified MEMAP in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of MEMAP including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of MEMAP may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of MEMAP including, but not limited to, those listed above.

In a further embodiment, an antagonist of MEMAP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of MEMAP. Examples of such disorders include, but are not limited to, those cell proliferative, autoimmune/inflammatory, neurological and gastrointestinal disorders described above. In one aspect, an antibody which specifically binds MEMAP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express MEMAP.

In an additional embodiment, a vector expressing the complement of the polynucleotide

encoding MEMAP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of MEMAP including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate
5 therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

10 An antagonist of MEMAP may be produced using methods which are generally known in the art. In particular, purified MEMAP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind MEMAP. Antibodies to MEMAP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments,
15 and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans,
and others may be immunized by injection with MEMAP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be
20 used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to
25 MEMAP have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein. Short stretches of MEMAP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

30 Monoclonal antibodies to MEMAP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and
35 Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce MEMAP-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for MEMAP may also be generated. For example, such fragments include, but are not limited to, $F(ab')_2$ fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between MEMAP and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering MEMAP epitopes is generally used, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for MEMAP. Affinity is expressed as an association constant, K_a , which is defined as the molar concentration of MEMAP-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple MEMAP epitopes, represents the average affinity, or avidity, of the antibodies for MEMAP. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular MEMAP epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in

which the MEMAP-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of MEMAP, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical

- 5 Approach, IRL Press, Washington DC; Liddell, J.E. and A. Cryer (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is generally employed in procedures requiring precipitation of MEMAP-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al., supra.)

In another embodiment of the invention, the polynucleotides encoding MEMAP, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, modifications of gene expression can be achieved by designing complementary sequences or antisense molecules (DNA, RNA, PNA, or modified oligonucleotides) to the coding or regulatory regions of the gene encoding MEMAP. Such technology is well known in the art, and antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding MEMAP. (See, e.g., Agrawal, S., ed. (1996) Antisense Therapeutics, Humana Press Inc., Totawa NJ.)

In therapeutic use, any gene delivery system suitable for introduction of the antisense sequences into appropriate target cells can be used. Antisense sequences can be delivered intracellularly in the form of an expression plasmid which, upon transcription, produces a sequence complementary to at least a portion of the cellular sequence encoding the target protein. (See, e.g., Slater, J.E. et al. (1998) *J. Allergy Clin. Immunol.* 102(3):469-475; and Scanlon, K.J. et al. (1995) 9(13):1288-1296.) Antisense sequences can also be introduced intracellularly through the use of viral vectors, such as retrovirus and adeno-associated virus vectors. (See, e.g., Miller, A.D. (1990) *Blood* 76:271; Ausubel, supra; Uckert, W. and W. Walther (1994) *Pharmacol. Ther.* 63(3):323-347.) Other gene delivery mechanisms include liposome-derived systems, artificial viral envelopes, and other systems known in the art. (See, e.g., Rossi, J.J. (1995) *Br. Med. Bull.* 51(1):217-225; Boado, R.J. et al. (1998) *J. Pharm. Sci.* 87(11):1308-1315; and Morris, M.C. et al. (1997) *Nucleic Acids Res.* 25(14):2730-2736.)

In another embodiment of the invention, polynucleotides encoding MEMAP may be used for somatic or germline gene therapy. Gene therapy may be performed to (i) correct a genetic deficiency

(e.g., in the cases of severe combined immunodeficiency (SCID)-X1 disease characterized by X-linked inheritance (Cavazzana-Calvo, M. et al. (2000) Science 288:669-672), severe combined immunodeficiency syndrome associated with an inherited adenosine deaminase (ADA) deficiency (Blaese, R.M. et al. (1995) Science 270:475-480; Bordignon, C. et al. (1995) Science 270:470-475), cystic fibrosis (Zabner, J. et al. (1993) Cell 75:207-216; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:643-666; Crystal, R.G. et al. (1995) Hum. Gene Therapy 6:667-703), thalassemias, familial hypercholesterolemia, and hemophilia resulting from Factor VIII or Factor IX deficiencies (Crystal, R.G. (1995) Science 270:404-410; Verma, I.M. and N. Somia (1997) Nature 389:239-242)), (ii) express a conditionally lethal gene product (e.g., in the case of cancers which result from unregulated cell proliferation), or (iii) express a protein which affords protection against intracellular parasites (e.g., against human retroviruses, such as human immunodeficiency virus (HIV) (Baltimore, D. (1988) Nature 335:395-396; Poeschla, E. et al. (1996) Proc. Natl. Acad. Sci. USA. 93:11395-11399), hepatitis B or C virus (HBV, HCV); fungal parasites, such as Candida albicans and Paracoccidioides brasiliensis; and protozoan parasites such as Plasmodium falciparum and Trypanosoma cruzi). In the case where a genetic deficiency in MEMAP expression or regulation causes disease, the expression of MEMAP from an appropriate population of transduced cells may alleviate the clinical manifestations caused by the genetic deficiency.

In a further embodiment of the invention, diseases or disorders caused by deficiencies in MEMAP are treated by constructing mammalian expression vectors encoding MEMAP and introducing these vectors by mechanical means into MEMAP-deficient cells. Mechanical transfer technologies for use with cells in vivo or ex vitro include (i) direct DNA microinjection into individual cells, (ii) ballistic gold particle delivery, (iii) liposome-mediated transfection, (iv) receptor-mediated gene transfer, and (v) the use of DNA transposons (Morgan, R.A. and W.F. Anderson (1993) Annu. Rev. Biochem. 62:191-217; Ivics, Z. (1997) Cell 91:501-510; Boulay, J-L. and H. Récipon (1998) Curr. Opin. Biotechnol. 9:445-450).

Expression vectors that may be effective for the expression of MEMAP include, but are not limited to, the PCDNA 3.1, EPITAG, PRCCMV2, PREP, PVAX vectors (Invitrogen, Carlsbad CA), PCMV-SCRIPT, PCMV-TAG, PEGSH/PERV (Stratagene, La Jolla CA), and PTET-OFF, PTET-ON, PTRE2, PTRE2-LUC, PTK-HYG (Clontech, Palo Alto CA). MEMAP may be expressed using (i) a constitutively active promoter, (e.g., from cytomegalovirus (CMV), Rous sarcoma virus (RSV), SV40 virus, thymidine kinase (TK), or β -actin genes), (ii) an inducible promoter (e.g., the tetracycline-regulated promoter (Gossen, M. and H. Bujard (1992) Proc. Natl. Acad. Sci. USA 89:5547-5551; Gossen, M. et al. (1995) Science 268:1766-1769; Rossi, F.M.V. and H.M. Blau (1998) Curr. Opin. Biotechnol. 9:451-456), commercially available in the T-REX plasmid (Invitrogen)); the ecdysone-inducible promoter (available in the plasmids PVGRXR and PIND; Invitrogen); the

FK506/rapamycin inducible promoter; or the RU486/mifepristone inducible promoter (Rossi, F.M.V. and H.M. Blau, *supra*), or (iii) a tissue-specific promoter or the native promoter of the endogenous gene encoding MEMAP from a normal individual.

Commercially available liposome transformation kits (e.g., the PERFECT LIPID TRANSFECTION KIT, available from Invitrogen) allow one with ordinary skill in the art to deliver polynucleotides to target cells in culture and require minimal effort to optimize experimental parameters. In the alternative, transformation is performed using the calcium phosphate method (Graham, F.L. and A.J. Eb (1973) *Virology* 52:456-467), or by electroporation (Neumann, E. et al. (1982) *EMBO J.* 1:841-845). The introduction of DNA to primary cells requires modification of these standardized mammalian transfection protocols.

In another embodiment of the invention, diseases or disorders caused by genetic defects with respect to MEMAP expression are treated by constructing a retrovirus vector consisting of (i) the polynucleotide encoding MEMAP under the control of an independent promoter or the retrovirus long terminal repeat (LTR) promoter, (ii) appropriate RNA packaging signals, and (iii) a Rev-responsive element (RRE) along with additional retrovirus *cis*-acting RNA sequences and coding sequences required for efficient vector propagation. Retrovirus vectors (e.g., PFB and PFBNEO) are commercially available (Stratagene) and are based on published data (Riviere, I. et al. (1995) *Proc. Natl. Acad. Sci. USA* 92:6733-6737), incorporated by reference herein. The vector is propagated in an appropriate vector-producing cell line (VPCL) that expresses an envelope gene with a tropism for receptors on the target cells or a promiscuous envelope protein such as VSVg (Armentano, D. et al. (1987) *J. Virol.* 61:1647-1650; Bender, M.A. et al. (1987) *J. Virol.* 61:1639-1646; Adam, M.A. and A.D. Miller (1988) *J. Virol.* 62:3802-3806; Dull, T. et al. (1998) *J. Virol.* 72:8463-8471; Zufferey, R. et al. (1998) *J. Virol.* 72:9873-9880). U.S. Patent Number 5,910,434 to Rigg ("Method for obtaining retrovirus packaging cell lines producing high transducing efficiency retroviral supernatant") discloses a method for obtaining retrovirus packaging cell lines and is hereby incorporated by reference. Propagation of retrovirus vectors, transduction of a population of cells (e.g., CD4⁺ T-cells), and the return of transduced cells to a patient are procedures well known to persons skilled in the art of gene therapy and have been well documented (Ranga, U. et al. (1997) *J. Virol.* 71:7020-7029; Bauer, G. et al. (1997) *Blood* 89:2259-2267; Bonyhadi, M.L. (1997) *J. Virol.* 71:4707-4716; Ranga, U. et al. (1998) *Proc. Natl. Acad. Sci. USA* 95:1201-1206; Su, L. (1997) *Blood* 89:2283-2290).

In the alternative, an adenovirus-based gene therapy delivery system is used to deliver polynucleotides encoding MEMAP to cells which have one or more genetic abnormalities with respect to the expression of MEMAP. The construction and packaging of adenovirus-based vectors are well known to those with ordinary skill in the art. Replication defective adenovirus vectors have

proven to be versatile for importing genes encoding immunoregulatory proteins into intact islets in the pancreas (Csete, M.E. et al. (1995) *Transplantation* 27:263-268). Potentially useful adenoviral vectors are described in U.S. Patent Number 5,707,618 to Armentano ("Adenovirus vectors for gene therapy"), hereby incorporated by reference. For adenoviral vectors, see also Antinozzi, P.A. et al. 5 (1999) *Annu. Rev. Nutr.* 19:511-544; and Verma, I.M. and N. Somia (1997) *Nature* 18:389:239-242, both incorporated by reference herein.

In another alternative, a herpes-based, gene therapy delivery system is used to deliver polynucleotides encoding MEMAP to target cells which have one or more genetic abnormalities with respect to the expression of MEMAP. The use of herpes simplex virus (HSV)-based vectors may be 10 especially valuable for introducing MEMAP to cells of the central nervous system, for which HSV has a tropism. The construction and packaging of herpes-based vectors are well known to those with ordinary skill in the art. A replication-competent herpes simplex virus (HSV) type 1-based vector has been used to deliver a reporter gene to the eyes of primates (Liu, X. et al. (1999) *Exp. Eye Res.* 169:385-395). The construction of a HSV-1 virus vector has also been disclosed in detail in U.S. 15 Patent Number 5,804,413 to DeLuca ("Herpes simplex virus strains for gene transfer"), which is hereby incorporated by reference. U.S. Patent Number 5,804,413 teaches the use of recombinant HSV d92 which consists of a genome containing at least one exogenous gene to be transferred to a cell under the control of the appropriate promoter for purposes including human gene therapy. Also taught by this patent are the construction and use of recombinant HSV strains deleted for ICP4, ICP27 20 and ICP22. For HSV vectors, see also Goins, W.F. et al. (1999) *J. Virol.* 73:519-532 and Xu, H. et al. (1994) *Dev. Biol.* 163:152-161, hereby incorporated by reference. The manipulation of cloned herpesvirus sequences, the generation of recombinant virus following the transfection of multiple plasmids containing different segments of the large herpesvirus genomes, the growth and propagation of herpesvirus, and the infection of cells with herpesvirus are techniques well known to those of 25 ordinary skill in the art.

In another alternative, an alphavirus (positive, single-stranded RNA virus) vector is used to deliver polynucleotides encoding MEMAP to target cells. The biology of the prototypic alphavirus, Semliki Forest Virus (SFV), has been studied extensively and gene transfer vectors have been based on the SFV genome (Garoff, H. and K.-J. Li (1998) *Curr. Opin. Biotechnol.* 9:464-469). During 30 alphavirus RNA replication, a subgenomic RNA is generated that normally encodes the viral capsid proteins. This subgenomic RNA replicates to higher levels than the full-length genomic RNA, resulting in the overproduction of capsid proteins relative to the viral proteins with enzymatic activity (e.g., protease and polymerase). Similarly, inserting the coding sequence for MEMAP into the alphavirus genome in place of the capsid-coding region results in the production of a large number of 35 MEMAP-coding RNAs and the synthesis of high levels of MEMAP in vector transduced cells. While

alphavirus infection is typically associated with cell lysis within a few days, the ability to establish a persistent infection in hamster normal kidney cells (BHK-21) with a variant of Sindbis virus (SIN) indicates that the lytic replication of alphaviruses can be altered to suit the needs of the gene therapy application (Dryga, S.A. et al. (1997) Virology 228:74-83). The wide host range of alphaviruses will allow the introduction of MEMAP into a variety of cell types. The specific transduction of a subset of cells in a population may require the sorting of cells prior to transduction. The methods of manipulating infectious cDNA clones of alphaviruses, performing alphavirus cDNA and RNA transfections, and performing alphavirus infections, are well known to those with ordinary skill in the art.

Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, may also be employed to inhibit gene expression. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding MEMAP.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding MEMAP. Such DNA sequences may be incorporated into a wide variety of

vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible
5 modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine,
10 cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

An additional embodiment of the invention encompasses a method for screening for a compound which is effective in altering expression of a polynucleotide encoding MEMAP. Compounds which may be effective in altering expression of a specific polynucleotide may include,
15 but are not limited to, oligonucleotides, antisense oligonucleotides, triple helix-forming oligonucleotides, transcription factors and other polypeptide transcriptional regulators, and non-macromolecular chemical entities which are capable of interacting with specific polynucleotide sequences. Effective compounds may alter polynucleotide expression by acting as either inhibitors or promoters of polynucleotide expression. Thus, in the treatment of disorders associated with increased
20 MEMAP expression or activity, a compound which specifically inhibits expression of the polynucleotide encoding MEMAP may be therapeutically useful, and in the treatment of disorders associated with decreased MEMAP expression or activity, a compound which specifically promotes expression of the polynucleotide encoding MEMAP may be therapeutically useful.

At least one, and up to a plurality, of test compounds may be screened for effectiveness in
25 altering expression of a specific polynucleotide. A test compound may be obtained by any method commonly known in the art, including chemical modification of a compound known to be effective in altering polynucleotide expression; selection from an existing, commercially-available or proprietary library of naturally-occurring or non-natural chemical compounds; rational design of a compound based on chemical and/or structural properties of the target polynucleotide; and selection from a
30 library of chemical compounds created combinatorially or randomly. A sample comprising a polynucleotide encoding MEMAP is exposed to at least one test compound thus obtained. The sample may comprise, for example, an intact or permeabilized cell, or an *in vitro* cell-free or reconstituted biochemical system. Alterations in the expression of a polynucleotide encoding MEMAP are assayed by any method commonly known in the art. Typically, the expression of a
35 specific nucleotide is detected by hybridization with a probe having a nucleotide sequence

complementary to the sequence of the polynucleotide encoding MEMAP. The amount of hybridization may be quantified, thus forming the basis for a comparison of the expression of the polynucleotide both with and without exposure to one or more test compounds. Detection of a change in the expression of a polynucleotide exposed to a test compound indicates that the test compound is effective in altering the expression of the polynucleotide. A screen for a compound effective in altering expression of a specific polynucleotide can be carried out, for example, using a Schizosaccharomyces pombe gene expression system (Atkins, D. et al. (1999) U.S. Patent No. 5,932,435; Arndt, G.M. et al. (2000) Nucleic Acids Res. 28:E15) or a human cell line such as HeLa cell (Clarke, M.L. et al. (2000) Biochem. Biophys. Res. Commun. 268:8-13). A particular embodiment of the present invention involves screening a combinatorial library of oligonucleotides (such as deoxyribonucleotides, ribonucleotides, peptide nucleic acids, and modified oligonucleotides) for antisense activity against a specific polynucleotide sequence (Bruice, T.W. et al. (1997) U.S. Patent No. 5,686,242; Bruice, T.W. et al. (2000) U.S. Patent No. 6,022,691).

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

An additional embodiment of the invention relates to the administration of a composition which generally comprises an active ingredient formulated with a pharmaceutically acceptable excipient. Excipients may include, for example, sugars, starches, celluloses, gums, and proteins. Various formulations are commonly known and are thoroughly discussed in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA). Such compositions may consist of MEMAP, antibodies to MEMAP, and mimetics, agonists, antagonists, or inhibitors of MEMAP.

The compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, pulmonary, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

Compositions for pulmonary administration may be prepared in liquid or dry powder form. These compositions are generally aerosolized immediately prior to inhalation by the patient. In the

case of small molecules (e.g. traditional low molecular weight organic drugs), aerosol delivery of fast-acting formulations is well-known in the art. In the case of macromolecules (e.g. larger peptides and proteins), recent developments in the field of pulmonary delivery via the alveolar region of the lung have enabled the practical delivery of drugs such as insulin to blood circulation (see, e.g., Patton, J.S. et al., U.S. Patent No. 5,997,848). Pulmonary delivery has the advantage of administration without needle injection, and obviates the need for potentially toxic penetration enhancers.

Compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

Specialized forms of compositions may be prepared for direct intracellular delivery of macromolecules comprising MEMAP or fragments thereof. For example, liposome preparations containing a cell-impermeable macromolecule may promote cell fusion and intracellular delivery of the macromolecule. Alternatively, MEMAP or a fragment thereof may be joined to a short cationic N-terminal portion from the HIV Tat-1 protein. Fusion proteins thus generated have been found to transduce into the cells of all tissues, including the brain, in a mouse model system (Schwarze, S.R. et al. (1999) Science 285:1569-1572).

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, monkeys, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example MEMAP or fragments thereof, antibodies of MEMAP, and agonists, antagonists or inhibitors of MEMAP, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the

active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1 μg to 100,000 μg , up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

In another embodiment, antibodies which specifically bind MEMAP may be used for the diagnosis of disorders characterized by expression of MEMAP, or in assays to monitor patients being treated with MEMAP or agonists, antagonists, or inhibitors of MEMAP. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for MEMAP include methods which utilize the antibody and a label to detect MEMAP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring MEMAP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of MEMAP expression. Normal or standard values for MEMAP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, for example, human subjects, with antibody to MEMAP under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of MEMAP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding MEMAP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of MEMAP may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess

expression of MEMAP, and to monitor regulation of MEMAP levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding MEMAP or closely related molecules may be used to identify nucleic acid sequences which encode MEMAP. The specificity of the probe, whether
5 it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding MEMAP, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and may have at least 50%
10 sequence identity to any of the MEMAP encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:38-74 or from genomic sequences including promoters, enhancers, and introns of the MEMAP gene.

Means for producing specific hybridization probes for DNAs encoding MEMAP include the cloning of polynucleotide sequences encoding MEMAP or MEMAP derivatives into vectors for the
15 production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes *in vitro* by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as ³²P or ³⁵S, or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

20 Polynucleotide sequences encoding MEMAP may be used for the diagnosis of disorders associated with expression of MEMAP. Examples of such disorders include, but are not limited to, a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including
25 adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an autoimmune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS),
30 Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis,
35 erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves'

disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and

5 extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders,

10 progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the

15 nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic,

20 endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, seasonal affective disorder (SAD), akathisia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, Tourette's disorder, progressive supranuclear palsy, corticobasal degeneration, and familial frontotemporal dementia; and a gastrointestinal disorder such as dysphagia, peptic esophagitis,

25 esophageal spasm, esophageal stricture, esophageal carcinoma, dyspepsia, indigestion, gastritis, gastric carcinoma, anorexia, nausea, emesis, gastroparesis, antral or pyloric edema, abdominal angina, pyrosis, gastroenteritis, intestinal obstruction, infections of the intestinal tract, peptic ulcer, cholelithiasis, cholecystitis, cholestasis, pancreatitis, pancreatic carcinoma, biliary tract disease, hepatitis, hyperbilirubinemia, cirrhosis, passive congestion of the liver, hepatoma, infectious colitis,

30 ulcerative colitis, ulcerative proctitis, Crohn's disease, Whipple's disease, Mallory-Weiss syndrome, colonic carcinoma, colonic obstruction, irritable bowel syndrome, short bowel syndrome, diarrhea, constipation, gastrointestinal hemorrhage, acquired immunodeficiency syndrome (AIDS) enteropathy, jaundice, hepatic encephalopathy, hepatorenal syndrome, hepatic steatosis, hemochromatosis, Wilson's disease, alpha₁-antitrypsin deficiency, Reye's syndrome, primary

35 sclerosing cholangitis, liver infarction, portal vein obstruction and thrombosis, centrilobular necrosis,

peliosis hepatis, hepatic vein thrombosis, veno-occlusive disease, preeclampsia, eclampsia, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, and hepatic tumors including nodular hyperplasias, adenomas, and carcinomas. The polynucleotide sequences encoding MEMAP may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR
5 technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered MEMAP expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding MEMAP may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide
10 sequences encoding MEMAP may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding MEMAP in the
15 sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of MEMAP, a normal or standard profile for expression is established. This may be accomplished by
20 combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding MEMAP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values
25 obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from
30 successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance
35 of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals

to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding MEMAP may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding MEMAP, or a fragment of a polynucleotide complementary to the polynucleotide encoding MEMAP, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantification of closely related DNA or RNA sequences.

In a particular aspect, oligonucleotide primers derived from the polynucleotide sequences encoding MEMAP may be used to detect single nucleotide polymorphisms (SNPs). SNPs are substitutions, insertions and deletions that are a frequent cause of inherited or acquired genetic disease in humans. Methods of SNP detection include, but are not limited to, single-stranded conformation polymorphism (SSCP) and fluorescent SSCP (fSSCP) methods. In SSCP, oligonucleotide primers derived from the polynucleotide sequences encoding MEMAP are used to amplify DNA using the polymerase chain reaction (PCR). The DNA may be derived, for example, from diseased or normal tissue, biopsy samples, bodily fluids, and the like. SNPs in the DNA cause differences in the secondary and tertiary structures of PCR products in single-stranded form, and these differences are detectable using gel electrophoresis in non-denaturing gels. In fSSCP, the oligonucleotide primers are fluorescently labeled, which allows detection of the amplimers in high-throughput equipment such as DNA sequencing machines. Additionally, sequence database analysis methods, termed *in silico* SNP (isSNP), are capable of identifying polymorphisms by comparing the sequence of individual overlapping DNA fragments which assemble into a common consensus sequence. These computer-based methods filter out sequence variations due to laboratory preparation of DNA and sequencing errors using statistical models and automated analyses of DNA sequence chromatograms. In the alternative, SNPs may be detected and characterized by mass spectrometry using, for example, the high throughput MASSARRAY system (Sequenom, Inc., San Diego CA).

Methods which may also be used to quantify the expression of MEMAP include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer or polynucleotide of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the

polynucleotide sequences described herein may be used as elements on a microarray. The microarray can be used in transcript imaging techniques which monitor the relative expression levels of large numbers of genes simultaneously as described in Seilhamer, J.J. et al., "Comparative Gene Transcript Analysis," U.S. Patent No. 5,840,484, incorporated herein by reference. The microarray may also be
5 used to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, to monitor progression/regression of disease as a function of gene expression, and to develop and monitor the activities of therapeutic agents in the treatment of disease. In particular, this information may be used to develop a pharmacogenomic profile of a patient in order to select the most appropriate
10 and effective treatment regimen for that patient. For example, therapeutic agents which are highly effective and display the fewest side effects may be selected for a patient based on his/her pharmacogenomic profile.

In another embodiment, antibodies specific for MEMAP, or MEMAP or fragments thereof may be used as elements on a microarray. The microarray may be used to monitor or measure
15 protein-protein interactions, drug-target interactions, and gene expression profiles, as described above.

A particular embodiment relates to the use of the polynucleotides of the present invention to generate a transcript image of a tissue or cell type. A transcript image represents the global pattern of gene expression by a particular tissue or cell type. Global gene expression patterns are analyzed by
20 quantifying the number of expressed genes and their relative abundance under given conditions and at a given time. (See Seilhamer et al., "Comparative Gene Transcript Analysis," U.S. Patent Number 5,840,484, expressly incorporated by reference herein.) Thus a transcript image may be generated by hybridizing the polynucleotides of the present invention or their complements to the totality of transcripts or reverse transcripts of a particular tissue or cell type. In one embodiment, the
25 hybridization takes place in high-throughput format, wherein the polynucleotides of the present invention or their complements comprise a subset of a plurality of elements on a microarray. The resultant transcript image would provide a profile of gene activity.

Transcript images may be generated using transcripts isolated from tissues, cell lines, biopsies, or other biological samples. The transcript image may thus reflect gene expression in vivo,
30 as in the case of a tissue or biopsy sample, or in vitro, as in the case of a cell line.

Transcript images which profile the expression of the polynucleotides of the present invention may also be used in conjunction with in vitro model systems and preclinical evaluation of pharmaceuticals, as well as toxicological testing of industrial and naturally-occurring environmental compounds. All compounds induce characteristic gene expression patterns, frequently termed
35 molecular fingerprints or toxicant signatures, which are indicative of mechanisms of action and

toxicity (Nuwaysir, E.F. et al. (1999) Mol. Carcinog. 24:153-159; Steiner, S. and N.L. Anderson (2000) Toxicol. Lett. 112-113:467-471, expressly incorporated by reference herein). If a test compound has a signature similar to that of a compound with known toxicity, it is likely to share those toxic properties. These fingerprints or signatures are most useful and refined when they contain expression information from a large number of genes and gene families. Ideally, a genome-wide measurement of expression provides the highest quality signature. Even genes whose expression is not altered by any tested compounds are important as well, as the levels of expression of these genes are used to normalize the rest of the expression data. The normalization procedure is useful for comparison of expression data after treatment with different compounds. While the assignment of gene function to elements of a toxicant signature aids in interpretation of toxicity mechanisms, knowledge of gene function is not necessary for the statistical matching of signatures which leads to prediction of toxicity. (See, for example, Press Release 00-02 from the National Institute of Environmental Health Sciences, released February 29, 2000, available at <http://www.niehs.nih.gov/oc/news/toxchip.htm>.) Therefore, it is important and desirable in toxicological screening using toxicant signatures to include all expressed gene sequences.

In one embodiment, the toxicity of a test compound is assessed by treating a biological sample containing nucleic acids with the test compound. Nucleic acids that are expressed in the treated biological sample are hybridized with one or more probes specific to the polynucleotides of the present invention, so that transcript levels corresponding to the polynucleotides of the present invention may be quantified. The transcript levels in the treated biological sample are compared with levels in an untreated biological sample. Differences in the transcript levels between the two samples are indicative of a toxic response caused by the test compound in the treated sample.

Another particular embodiment relates to the use of the polypeptide sequences of the present invention to analyze the proteome of a tissue or cell type. The term proteome refers to the global pattern of protein expression in a particular tissue or cell type. Each protein component of a proteome can be subjected individually to further analysis. Proteome expression patterns, or profiles, are analyzed by quantifying the number of expressed proteins and their relative abundance under given conditions and at a given time. A profile of a cell's proteome may thus be generated by separating and analyzing the polypeptides of a particular tissue or cell type. In one embodiment, the separation is achieved using two-dimensional gel electrophoresis, in which proteins from a sample are separated by isoelectric focusing in the first dimension, and then according to molecular weight by sodium dodecyl sulfate slab gel electrophoresis in the second dimension (Steiner and Anderson, *supra*). The proteins are visualized in the gel as discrete and uniquely positioned spots, typically by staining the gel with an agent such as Coomassie Blue or silver or fluorescent stains. The optical density of each protein spot is generally proportional to the level of the protein in the sample. The

optical densities of equivalently positioned protein spots from different samples, for example, from biological samples either treated or untreated with a test compound or therapeutic agent, are compared to identify any changes in protein spot density related to the treatment. The proteins in the spots are partially sequenced using, for example, standard methods employing chemical or enzymatic cleavage followed by mass spectrometry. The identity of the protein in a spot may be determined by comparing its partial sequence, preferably of at least 5 contiguous amino acid residues, to the polypeptide sequences of the present invention. In some cases, further sequence data may be obtained for definitive protein identification.

A proteomic profile may also be generated using antibodies specific for MEMAP to quantify the levels of MEMAP expression. In one embodiment, the antibodies are used as elements on a microarray, and protein expression levels are quantified by exposing the microarray to the sample and detecting the levels of protein bound to each array element (Lueking, A. et al. (1999) *Anal. Biochem.* 270:103-111; Mendoz, L.G. et al. (1999) *Biotechniques* 27:778-788). Detection may be performed by a variety of methods known in the art, for example, by reacting the proteins in the sample with a thiol- or amino-reactive fluorescent compound and detecting the amount of fluorescence bound at each array element.

Toxicant signatures at the proteome level are also useful for toxicological screening, and should be analyzed in parallel with toxicant signatures at the transcript level. There is a poor correlation between transcript and protein abundances for some proteins in some tissues (Anderson, N.L. and J. Seilhamer (1997) *Electrophoresis* 18:533-537), so proteome toxicant signatures may be useful in the analysis of compounds which do not significantly affect the transcript image, but which alter the proteomic profile. In addition, the analysis of transcripts in body fluids is difficult, due to rapid degradation of mRNA, so proteomic profiling may be more reliable and informative in such cases.

In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins that are expressed in the treated biological sample are separated so that the amount of each protein can be quantified. The amount of each protein is compared to the amount of the corresponding protein in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample. Individual proteins are identified by sequencing the amino acid residues of the individual proteins and comparing these partial sequences to the polypeptides of the present invention.

In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins from the biological sample are incubated with antibodies specific to the polypeptides of the present invention. The amount of

protein recognized by the antibodies is quantified. The amount of protein in the treated biological sample is compared with the amount in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample.

- 5 Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.) Various types of microarrays are
10 well known and thoroughly described in DNA Microarrays: A Practical Approach, M. Schena, ed. (1999) Oxford University Press, London, hereby expressly incorporated by reference.

- In another embodiment of the invention, nucleic acid sequences encoding MEMAP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. Either coding or noncoding sequences may be used, and in some instances, noncoding sequences may
15 be preferable over coding sequences. For example, conservation of a coding sequence among members of a multi-gene family may potentially cause undesired cross hybridization during chromosomal mapping. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes
20 (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.) Once mapped, the nucleic acid sequences of the invention may be used to develop genetic linkage maps, for example, which correlate the inheritance of a disease state with the inheritance of a particular chromosome region or restriction fragment length polymorphism
25 (RFLP). (See, e.g., Lander, E.S. and D. Botstein (1986) Proc. Natl. Acad. Sci. USA 83:7353-7357.)

- Fluorescent in situ hybridization (FISH) may be correlated with other physical and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) World Wide Web site. Correlation between the location of the gene encoding MEMAP on a
30 physical map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder and thus may further positional cloning efforts.

- In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse,
35 may reveal associated markers even if the exact chromosomal locus is not known. This information is

valuable to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the gene or genes responsible for a disease or syndrome have been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further
5 investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the instant invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, MEMAP, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug
10 screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between MEMAP and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT
15 application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with MEMAP, or fragments thereof, and washed. Bound MEMAP is then detected by methods well known in the art. Purified MEMAP can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a
20 solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding MEMAP specifically compete with a test compound for binding MEMAP. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with MEMAP.

25 In additional embodiments, the nucleotide sequences which encode MEMAP may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding
30 description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. 60/149,641 and U.S. Ser. No. 60/164,203 are hereby expressly incorporated
35 by reference.

EXAMPLES

I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies); a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A⁺) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERScript plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), PSORT1 plasmid (Life Technologies), pcDNA2.1 plasmid (Invitrogen, Carlsbad CA), or pINCY plasmid (Incyte Genomics, Palo Alto CA). Recombinant plasmids were transformed into competent *E. coli* cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5 α , DH10B, or ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids obtained as described in Example I were recovered from host cells by in vivo excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1

ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

Incyte cDNA recovered in plasmids as described in Example II were sequenced as follows.

Sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (PE Biosystems) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (PE Biosystems). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing system (PE Biosystems) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example VI.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions, references, and threshold parameters. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments were generated using the default parameters specified by the clustal algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned

sequences.

The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programming, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and PFAM to acquire annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA.

The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:38-74. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

IV. Analysis of Polynucleotide Expression

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in cDNA databases such as GenBank or LIFESEQ (Incyte Genomics). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\text{BLAST Score} \times \text{Percent Identity}}{5 \times \text{minimum \{length(Seq. 1), length(Seq. 2)\}}}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. The product score is a normalized value between 0 and 100, and is calculated as follows: the BLAST score is multiplied by the percent nucleotide identity and the

product is divided by (5 times the length of the shorter of the two sequences). The BLAST score is calculated by assigning a score of +5 for every base that matches in a high-scoring segment pair (HSP), and -4 for every mismatch. Two sequences may share more than one HSP (separated by gaps). If there is more than one HSP, then the pair with the highest BLAST score is used to calculate the product score. The product score represents a balance between fractional overlap and quality in a BLAST alignment. For example, a product score of 100 is produced only for 100% identity over the entire length of the shorter of the two sequences being compared. A product score of 70 is produced either by 100% identity and 70% overlap at one end, or by 88% identity and 100% overlap at the other. A product score of 50 is produced either by 100% identity and 50% overlap at one end, or 79% identity and 100% overlap.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding MEMAP occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation, trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

20 V. Chromosomal Mapping of MEMAP Encoding Polynucleotides

The cDNA sequences which were used to assemble SEQ ID NO:38-74 were compared with sequences from the Incyte LIFESEQ database and public domain databases using BLAST and other implementations of the Smith-Waterman algorithm. Sequences from these databases that matched SEQ ID NO:38-74 were assembled into clusters of contiguous and overlapping sequences using assembly algorithms such as Phrap (Table 5). Radiation hybrid and genetic mapping data available from public resources such as the Stanford Human Genome Center (SHGC), Whitehead Institute for Genome Research (WIGR), and Génethon were used to determine if any of the clustered sequences had been previously mapped. Inclusion of a mapped sequence in a cluster resulted in the assignment of all sequences of that cluster, including its particular SEQ ID NO., to that map location.

30 The genetic map locations of SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:60, SEQ ID NO:63, and SEQ ID NO:67 are described in The Invention as ranges, or intervals, of human chromosomes. More than one map location is reported for SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:44, SEQ ID NO:60, and SEQ ID NO:63, indicating that previously mapped sequences having similarity, but not complete identity, to SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:44, SEQ ID NO:60, and SEQ ID NO:63 were assembled into their respective

clusters. The map position of an interval, in centiMorgans, is measured relative to the terminus of the chromosome's p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.)

5 The cM distances are based on genetic markers mapped by Généthon which provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters. Diseases associated with the public and Incyte sequences located within the indicated intervals are also reported in the Invention where applicable. Human genome maps and other resources available to the public, such as the NCBI "GeneMap'99" World Wide Web site (<http://www.ncbi.nlm.nih.gov/genemap/>), can be

10 employed to determine if previously identified disease genes map within or in proximity to the intervals indicated above.

VI. Extension of MEMAP Encoding Polynucleotides

The full length nucleic acid sequences of SEQ ID NO:38-74 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this

15 fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length; to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would

20 result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction

25 mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+} , $(NH_4)_2SO_4$, and β -mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the

30 alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 μ l PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE

35 and 0.5 μ l of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar,

Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 μ l to 10 μ l aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent *E. coli* cells. Transformed cells were selected on antibiotic-containing media, and individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3-min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethylsulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (PE Biosystems).

In like manner, the polynucleotide sequences of SEQ ID NO:38-74 are used to obtain 5' regulatory sequences using the procedure above, along with oligonucleotides designed for such extension, and an appropriate genomic library.

VII. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:38-74 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μ Ci of [γ -³²P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a

SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10^7 counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

- 5 The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and
10 compared.

VIII. Microarrays

- The linkage or synthesis of array elements upon a microarray can be achieved utilizing photolithography, piezoelectric printing (ink-jet printing, See, e.g., Baldeschweiler, supra), mechanical microspotting technologies, and derivatives thereof. The substrate in each of the
15 aforementioned technologies should be uniform and solid with a non-porous surface (Skena (1999), supra). Suggested substrates include silicon, silica, glass slides, glass chips, and silicon wafers. Alternatively, a procedure analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced using available methods and machines well known to
20 those of ordinary skill in the art and may contain any appropriate number of elements. (See, e.g., Skena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645; Marshall, A. and J. Hodgson (1998) Nat. Biotechnol. 16:27-31.)

- Full length cDNAs, Expressed Sequence Tags (ESTs), or fragments or oligomers thereof may comprise the elements of the microarray. Fragments or oligomers suitable for hybridization can be
25 selected using software well known in the art such as LASERGENE software (DNASTAR). The array elements are hybridized with polynucleotides in a biological sample. The polynucleotides in the biological sample are conjugated to a fluorescent label or other molecular tag for ease of detection. After hybridization, nonhybridized nucleotides from the biological sample are removed, and a fluorescence scanner is used to detect hybridization at each array element. Alternatively, laser
30 desorption and mass spectrometry may be used for detection of hybridization. The degree of complementarity and the relative abundance of each polynucleotide which hybridizes to an element on the microarray may be assessed. In one embodiment, microarray preparation and usage is described in detail below.

Tissue or Cell Sample Preparation

- 35 Total RNA is isolated from tissue samples using the guanidinium thiocyanate method and

poly(A)⁺ RNA is purified using the oligo-(dT) cellulose method. Each poly(A)⁺ RNA sample is reverse transcribed using MMLV reverse-transcriptase, 0.05 pg/μl oligo-(dT) primer (21mer), 1X first strand buffer, 0.03 units/μl RNase inhibitor, 500 μM dATP, 500 μM dGTP, 500 μM dTTP, 40 μM dCTP, 40 μM dCTP-Cy3 (BDS) or dCTP-Cy5 (Amersham Pharmacia Biotech). The reverse transcription reaction is performed in a 25 ml volume containing 200 ng poly(A)⁺ RNA with GEMBRIGHT kits (Incyte). Specific control poly(A)⁺ RNAs are synthesized by in vitro transcription from non-coding yeast genomic DNA. After incubation at 37 °C for 2 hr, each reaction sample (one with Cy3 and another with Cy5 labeling) is treated with 2.5 ml of 0.5M sodium hydroxide and incubated for 20 minutes at 85 °C to stop the reaction and degrade the RNA. Samples are purified using two successive CHROMA SPIN 30 gel filtration spin columns (CLONTECH Laboratories, Inc. (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated using 1 ml of glycogen (1 mg/ml), 60 ml sodium acetate, and 300 ml of 100% ethanol. The sample is then dried to completion using a SpeedVAC (Savant Instruments Inc., Holbrook NY) and resuspended in 14 μl 5X SSC/0.2% SDS.

15 Microarray Preparation

Sequences of the present invention are used to generate array elements. Each array element is amplified from bacterial cells containing vectors with cloned cDNA inserts. PCR amplification uses primers complementary to the vector sequences flanking the cDNA insert. Array elements are amplified in thirty cycles of PCR from an initial quantity of 1-2 ng to a final quantity greater than 5 μg. Amplified array elements are then purified using SEPHACRYL-400 (Amersham Pharmacia Biotech).

Purified array elements are immobilized on polymer-coated glass slides. Glass microscope slides (Corning) are cleaned by ultrasound in 0.1% SDS and acetone, with extensive distilled water washes between and after treatments. Glass slides are etched in 4% hydrofluoric acid (VWR Scientific Products Corporation (VWR), West Chester PA), washed extensively in distilled water, and coated with 0.05% aminopropyl silane (Sigma) in 95% ethanol. Coated slides are cured in a 110°C oven.

Array elements are applied to the coated glass substrate using a procedure described in US Patent No. 5,807,522, incorporated herein by reference. 1 μl of the array element DNA, at an average concentration of 100 ng/μl, is loaded into the open capillary printing element by a high-speed robotic apparatus. The apparatus then deposits about 5 nl of array element sample per slide.

Microarrays are UV-crosslinked using a STRATALINKER UV-crosslinker (Stratagene). Microarrays are washed at room temperature once in 0.2% SDS and three times in distilled water. Non-specific binding sites are blocked by incubation of microarrays in 0.2% casein in phosphate buffered saline (PBS) (Tropix, Inc., Bedford MA) for 30 minutes at 60 °C followed by washes in

0.2% SDS and distilled water as before.

Hybridization

Hybridization reactions contain 9 μ l of sample mixture consisting of 0.2 μ g each of Cy3 and Cy5 labeled cDNA synthesis products in 5X SSC, 0.2% SDS hybridization buffer. The sample mixture is heated to 65 °C for 5 minutes and is aliquoted onto the microarray surface and covered with an 1.8 cm² coverslip. The arrays are transferred to a waterproof chamber having a cavity just slightly larger than a microscope slide. The chamber is kept at 100% humidity internally by the addition of 140 μ l of 5X SSC in a corner of the chamber. The chamber containing the arrays is incubated for about 6.5 hours at 60 °C. The arrays are washed for 10 min at 45 °C in a first wash buffer (1X SSC, 0.1% SDS), three times for 10 minutes each at 45 °C in a second wash buffer (0.1X SSC), and dried.

Detection

Reporter-labeled hybridization complexes are detected with a microscope equipped with an Innova 70 mixed gas 10 W laser (Coherent, Inc., Santa Clara CA) capable of generating spectral lines at 488 nm for excitation of Cy3 and at 632 nm for excitation of Cy5. The excitation laser light is focused on the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide containing the array is placed on a computer-controlled X-Y stage on the microscope and raster-scanned past the objective. The 1.8 cm x 1.8 cm array used in the present example is scanned with a resolution of 20 micrometers.

In two separate scans, a mixed gas multiline laser excites the two fluorophores sequentially. Emitted light is split, based on wavelength, into two photomultiplier tube detectors (PMT R1477, Hamamatsu Photonics Systems, Bridgewater NJ) corresponding to the two fluorophores. Appropriate filters positioned between the array and the photomultiplier tubes are used to filter the signals. The emission maxima of the fluorophores used are 565 nm for Cy3 and 650 nm for Cy5. Each array is typically scanned twice, one scan per fluorophore using the appropriate filters at the laser source, although the apparatus is capable of recording the spectra from both fluorophores simultaneously.

The sensitivity of the scans is typically calibrated using the signal intensity generated by a cDNA control species added to the sample mixture at a known concentration. A specific location on the array contains a complementary DNA sequence, allowing the intensity of the signal at that location to be correlated with a weight ratio of hybridizing species of 1:100,000. When two samples from different sources (e.g., representing test and control cells), each labeled with a different fluorophore, are hybridized to a single array for the purpose of identifying genes that are differentially expressed, the calibration is done by labeling samples of the calibrating cDNA with the two fluorophores and adding identical amounts of each to the hybridization mixture.

The output of the photomultiplier tube is digitized using a 12-bit RTI-835H analog-to-digital

(A/D) conversion board (Analog Devices, Inc., Norwood MA) installed in an IBM-compatible PC computer. The digitized data are displayed as an image where the signal intensity is mapped using a linear 20-color transformation to a pseudocolor scale ranging from blue (low signal) to red (high signal). The data is also analyzed quantitatively. Where two different fluorophores are excited and
5 measured simultaneously, the data are first corrected for optical crosstalk (due to overlapping emission spectra) between the fluorophores using each fluorophore's emission spectrum.

A grid is superimposed over the fluorescence signal image such that the signal from each spot is centered in each element of the grid. The fluorescence signal within each element is then integrated to obtain a numerical value corresponding to the average intensity of the signal. The
10 software used for signal analysis is the GEMTOOLS gene expression analysis program (Incyte).

IX. Complementary Polynucleotides

Sequences complementary to the MEMAP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring MEMAP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same
15 procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of MEMAP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the MEMAP-encoding
20 transcript.

X. Expression of MEMAP

Expression and purification of MEMAP is achieved using bacterial or virus-based expression systems. For expression of MEMAP in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA
25 transcription. Examples of such promoters include, but are not limited to, the *trp-lac (tac)* hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express MEMAP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of MEMAP in eukaryotic cells is achieved by infecting
30 insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding MEMAP by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to
35 infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases.

Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, MEMAP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from MEMAP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch. 10 and 16). Purified MEMAP obtained by these methods can be used directly in the assays shown in Examples XI and XV.

XI. Demonstration of MEMAP Activity

MEMAP activity is demonstrated using a generic immunoblotting strategy or through a MEMAP-specific activity assay as outlined below. As a general approach, cell lines or tissues transformed with a vector containing MEMAP coding sequences can be assayed for MEMAP activity by immunoblotting. Transformed cells are denatured in SDS in the presence of β -mercaptoethanol, nucleic acids are removed by ethanol precipitation, and proteins are purified by acetone precipitation. Pellets are resuspended in 20 mM Tris buffer at pH 7.5 and incubated with Protein G-Sepharose pre-coated with an antibody specific for MEMAP. After washing, the Sepharose beads are boiled in electrophoresis sample buffer, and the eluted proteins subjected to SDS-PAGE. Proteins are transferred from the SDS-PAGE gel to a membrane for immunoblotting, and the MEMAP activity is assessed by visualizing and quantifying bands on the blot using antibody specific for MEMAP as the primary antibody and ^{125}I -labeled IgG specific for the primary antibody as the secondary antibody.

A specific assay for MEMAP activity measures the expression of MEMAP on the cell surface. cDNA encoding MEMAP is transfected into a mammalian (non-human) cell line. Cell surface proteins are labeled with biotin as described in de la Fuente, M.A. et al. ((1997) Blood 90:2398-2405). Immunoprecipitations are performed using MEMAP-specific antibodies, and immunoprecipitated samples are analyzed using SDS-PAGE and immunoblotting techniques. The ratio of labeled immunoprecipitant to unlabeled immunoprecipitant is proportional to the amount of MEMAP expressed on the cell surface.

In an alternative specific assay, MEMAP transport activity is assayed by measuring uptake of

labeled substrates into Xenopus laevis oocytes. Oocytes at stages V and VI are injected with MEMAP mRNA (10 ng per oocyte) and incubated for 3 days at 18°C in OR2 medium (82.5mM NaCl, 2.5 mM KCl, 1mM CaCl₂, 1mM MgCl₂, 1mM Na₂HPO₄, 5 mM Hepes, 3.8 mM NaOH, 50µg/ml gentamycin, pH 7.8) to allow expression of MEMAP protein. Oocytes are then transferred to standard uptake medium (100mM NaCl, 2 mM KCl, 1mM CaCl₂, 1mM MgCl₂, 10 mM Hepes/Tris pH 7.5). Uptake of various substrates (e.g., amino acids, sugars, drugs, and neurotransmitters) is initiated by adding a ³H substrate to the oocytes. After incubating for 30 minutes, uptake is terminated by washing the oocytes three times in Na⁺-free medium, measuring the incorporated ³H, and comparing with controls. MEMAP activity is proportional to the level of internalized ³H substrate.

XII. Functional Assays

MEMAP function is assessed by expressing the sequences encoding MEMAP at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT plasmid (Life Technologies) and pCR3.1 plasmid (Invitrogen), both of which contain the cytomegalovirus promoter. 5-10 µg of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2 µg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of MEMAP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding MEMAP and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions

of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding MEMAP and other genes of interest can be analyzed by
5 northern analysis or microarray techniques.

XIII. Production of MEMAP Specific Antibodies

MEMAP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

10 Alternatively, the MEMAP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, *supra*, ch. 11.)

15 Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (PE Biosystems) using Fmoc chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, *supra*.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-
20 MEMAP activity by, for example, binding the peptide or MEMAP to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIV. Purification of Naturally Occurring MEMAP Using Specific Antibodies

Naturally occurring or recombinant MEMAP is substantially purified by immunoaffinity chromatography using antibodies specific for MEMAP. An immunoaffinity column is constructed by
25 covalently coupling anti-MEMAP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing MEMAP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of MEMAP (e.g., high ionic strength
30 buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/MEMAP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and MEMAP is collected.

XV. Identification of Molecules Which Interact with MEMAP

MEMAP, or biologically active fragments thereof, are labeled with ¹²⁵I Bolton-Hunter
35 reagent. (See, e.g., Bolton A.E. and W.M. Hunter (1973) *Biochem. J.* 133:529-539.) Candidate

molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled MEMAP, washed, and any wells with labeled MEMAP complex are assayed. Data obtained using different concentrations of MEMAP are used to calculate values for the number, affinity, and association of MEMAP with the candidate molecules.

5 Alternatively, molecules interacting with MEMAP are analyzed using the yeast two-hybrid system as described in Fields, S. and O. Song (1989, Nature 340:245-246), or using commercially available kits based on the two-hybrid system, such as the MATCHMAKER system (Clontech).

MEMAP may also be used in the PATHCALLING process (CuraGen Corp., New Haven CT) which employs the yeast two-hybrid system in a high-throughput manner to determine all interactions
10 between the proteins encoded by two large libraries of genes (Nandabalan, K. et al. (2000) U.S. Patent No. 6,057,101).

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the
15 invention. Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

Table 1

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	38	112301	PITUNOT01	003382R1 (HMC1NOT01), 094523R1 (PITUNOT01), 112301H1 (PITUNOT01), 301778X11 (TESTNOT04), 320551X13 (EOSIHET02), 1368852R1 (SCORNON02), 1800784H1 (COLNNOT27), 2117174X17C1 (BRSTTUT02), 2526345F6 (BRAITUT21), 4333609H1 (KIDCTWT01)
2	39	997947	KIDNTUT01	997947H1 (KIDNTUT01), 997947T6 (KIDNTUT01), 1417936X306D1 (KIDNNOT09), 1672062X307V1 (BLADNOT05), 3738956T6 (MENTNOT01), SCCA01437V1, SCCA05013V1, SCCA01691V1, SCCA02873V1
3	40	1521513	BLADTUT04	1222062H1 (NEUTGMT01), 1521513H1 (BLADTUT04), 1521513T1 (BLADTUT04), 3558522F6 (LUNGNOT31), 3558522T6 (LUNGNOT31)
4	41	1863994	PROSNOT19	265171R6 (HNT2AGT01), 1863994H1 (PROSNOT19), 3750444F6 (UTRSNOT18), 4177677F6 (BRAINOT22), 4697638F6 (BRALNOT01), 4774040F6 (BRAQNOT01), SCEA02960V1
5	42	2071941	ISLTNOT01	286350R1 (EOSIHET02), 491305R1 (HNT2AGT01), 724168R1 (SYNOOAT01), 1466668F1 (PANCUTUT02), 2071941H1 (ISLTNOT01), 2071941X11C1 (ISLTNOT01), 3579445H1 (293TF3T01)
6	43	2172512	ENDCNOT03	2172512H1 (ENDCNOT03), 2544419F6 (UTRSNOT11), 2798626H1 (NPOLNOT01), 3203359H1 (PENCNOT02), g1241299
7	44	2483172	SMCANOT01	217987F1 (STOMNOT01), 1289703F6 (BRAINOT11), 1289703T6 (BRAINOT11), 2211377F6 (SINFET03), 2483172H1 (SMCANOT01), 2493236H1 (ADRETUT05), 3274006F6 (PROSBPT06)

Table 1

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
8	45	2656128	THYMNOT04	2654722T6 (THYMNOT04), 2656128H1 (THYMNOT04), 2837168F6 (TLYMNOT03)
9	46	5855841	FIBAUNT02	894553T1 (BRSTNOT05), 1296289F1 (PGANNOT03), 1466541T1 (PANCUTUT02), 2046927F6 (THP1T7T01), 2058873R6 (OVARNOT03), 3800875F6 (SPLNNOT12), 5855841H1 (FIBAUNT02)
10	47	603462	BRSTTUT01	603462H1 (BRSTTUT01), 1487733H1 (UCMCL5T01), 1750451F6 (STOMTUT02), 5182853T6 (LUNGTMWT03)
11	48	747681	BRAITUT01	747681H1 (BRAITUT01), 752009R1 (BRAITUT01), 1267874F1 (BRAINOT09), 1833308R6 (BRAINON01), 2673538X19F1 (KIDNNOT19), SBCA07003F3, SCDA07521V1, SCDA04982V1, SCDA07275V1
12	49	919469	RATRNOT02	153337R6 (THP1PLB02), 1525415F6 (UCMCL5T01), 1527804F1 (UCMCL5T01), 1985565R6 (LUNGAST01), 2397811T6 (THPIAZT01), SARH01416F1, SARA03198F1
13	50	977658	BRSTNOT02	977658H1 (BRSTNOT02), 1873689F6 (LEUKNOT02), 2155095F6 (BRAINOT09), 2186432F6 (PROSNOT26), 2204117F6 (SPLNFET02), 2206291F6 (SPLNFET02), 3255048R6 (OVARUN01), 3501520H1 (ADRENOT11), 3743427H1 (THYMNOT08)
14	51	1004703	BRSTNOT03	742178H1 (PANCNOT04), 1444583F6 (THYRNOT03), 2068902X15C1 (ISLTNOT01), 2616367F6 (GBLANOT01), SBVA02190V1
15	52	1334051	COLNNOT13	3222815T6 (COLNNON03), SXBC00794V1, SXBC00639V1
16	53	1336728	COLNNOT13	630458R6 (KIDNNOT05), 1336728H1 (COLNNOT13), SXBC00758V1, SXBC01825V1, SXBC01531V1, SXBC01624V1, SXBC00128V1

Table 1

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
17	54	1452856	PENITUT01	873008R1 (LUNGAST01), 1452856H1 (PENITUT01), 2433573H1 (BRAVUNT02), 2444932F6 (THPINOT03), 2858295F6 (SININOT03)
18	55	1562471	SPLNNOT04	286237F1 (EOSIHET02), 1562471H1 (SPLNNOT04), 1880730F6 (LEUKNOT03), 3420608F6 (UCMCNOT04), SBWA00968V1, SXBC01387V1, SBWA02301V1
19	56	1618158	BRAITUT12	967563R1 (BRSTNOT05), 1618158H1 (BRAITUT12), 1785271F6 (BRAINOT10), 2074680F6 (ISLTNOT01), 2822196H1 (ADRETUT06)
20	57	1656935	URETTUT01	1656935F6 (URETTUT01), 1656935H1 (URETTUT01), 2827605F6 (TLYMNOT03), 5272146H1 (OVARINOT02), g1482116
21	58	1859305	PROSNOT18	079372F1 (SYNORAB01), 639845R1 (BRSTNOT03), 1859305H1 (PROSNOT18), 3328091F6 (HEAONOT04), 3354812F6 (PROSNOT28), 5510642H1 (BRADDIR01)
22	59	1949083	PITUNOT01	1287161H1 (BRAINOT11), 1949083H1 (PITUNOT01), 1949083R6 (PITUNOT01), 1949083T6 (PITUNOT01), 3814131F6 (TONSNOT03)
23	60	1996357	BRSTTUT03	260527R6 (HNT2RAT01), 260527T6 (HNT2RAT01), 1313441F1 (BLADTUT02), 1442781R1 (THYRNOT03), 1996357H1 (BRSTTUT03), 1996357T6 (BRSTTUT03), 4262451H1 (BSCNDIT02), SAZA00147F1
24	61	2061330	OVARNOT03	2061330H1 (OVARNOT03), 2724233T6 (LUNGUTUT10), 5104031T6 (PROSTUS20)
25	62	2346947	TESTTUT02	2346947F6 (TESTTUT02), 2346947H1 (TESTTUT02), 4051345F6 (SININOT18)

Table 1

Polyptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
26	63	2795577	NPOLNOT01	867213R6 (BRAITUT03), 2381770H1 (ISLTNOT01), 2795577CT1 (NPOLNOT01), 2795577H1 (NPOLNOT01)
27	64	3255825	OVARTUN01	3255825CT1 (OVARTUN01), 3255825H1 (OVARTUN01)
28	65	3393430	LUNGNOT28	2187169H1 (PROSNOT26), 3393256H1 (LUNGNOT28), 3393430H1 (LUNGNOT28), 3395774H1 (LUNGNOT28), 4689688H1 (LIVRTUT12), 4895996H1 (LIVRTUT12), 4896461F6 (LIVRTUT12), 4984527F6 (LIVRTUT10), 4992946H1 (LIVRTUT11)
29	66	3490990	EPIGNOT01	1235428F1 (LUNGFET03), 1662973T6 (BRSTNOT09), 2362021H1 (LUNGFET05), 2362021R6 (LUNGFET05), 3490990H1 (EPIGNOT01)
30	67	3635154	LIVRNOT03	027592H1 (SPLNFET01), 3635154H1 (LIVRNOT03), g1012932
31	68	4374347	CONFNOT03	860875X11 (BRAITUT03), 898143R6 (BRSTNOT05), 4374347H1 (CONFNOT03)
32	69	4596747	COLSTUT01	137213R1 (SYNORAB01), 545568R6 (OVARNOT02), 1235402F1 (LUNGFET03), 1268010F1 (BRAINOT09), 1271078F1 (TESTTUT02), 1301951F6 (BRSTNOT07), 1994442R6 (BRSTTUT03), 2343102H1 (TESTTUT02), 3274538F6 (PROSBPT06), 4596747H1 (COLSTUT01)
33	70	5052680	BRSTNOT33	1973688H1 (UCMCL5T01), 3926410F6 (KIDNNOT19), 4501839F6 (BRAVXT02), 5052680F6 (BRSTNOT33), 5052680H1 (BRSTNOT33), 5186780F6 (LUNGTMOT04)
34	71	5373575	BRAINOT22	262776T6 (HNT2AGT01), 1234057F1 (LUNGFET03), 1741526R6 (HIPONON01), 1871204F6 (SKINBIT01), 2192479F6 (THYRTUT03), 2556849H1 (THYMNOT03), 2722451T6 (LUNGTUT10), 4114985H1 (UTRSTUT07), 5373575H1 (BRAINOT22)

Table 1

Polypeptide SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
35	72	5524468	LIVRDIR01	4024068F6 (BRAXNOT02), 5524468H1 (LIVRDIR01), SXBC01952V1
36	73	5944279	COLADIT05	1662182H1 (BRSTNOT09), 1698677F6 (BLADTUT05), 1916639R6 (PROSNOT06), 1916639T6 (PROSNOT06), 2298565R6 (BRSTNOT05), 2298565T6 (BRSTNOT05), 2583019F6 (KIDNTUT13), 2870903F6 (THYRNOT10), 3970715H1 (PROSTUT10), 3971695H1 (PROSTUT10), 5944279H1 (COLADIT05)
37	74	6114480	SINITMT04	1579843F6 (DUODNOT01), 1579843T6 (DUODNOT01), 4181024T6 (SINITUT03), 6114480H1 (SINITMT04), SXBC000007V1, SXBC00504V1, SCSA05104V1

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
1	351	S31 T116 S169 T229 T2 S209 T306	N128	Signal peptide: M1-A33	Paraneoplastic neural antigen MA1 [Homo sapiens] g4104634	BLAST-GenBank MOTIFS SPSCAN
2	458	T198 S27 S37 T87 S251 S257 S325 S373 S405 S422 T454 T210 S228 S401 Y93	N75 N159 N279 N445	Signal peptide: M1-T24 Glycoprotein signature: C199-L448	Pancortin-3 [Mus musculus] g3218528	BLAST-GenBank MOTIFS SPSCAN HMMER BLAST-PRODOM
3	219	T51 S120 S163 T175 T181 S3 T12 T45 S75 S104 S128	N2 N62 N107	Signal peptide: M1-C42 Transmembrane domain: L32-F49 C-type lectin domain: C80-E206	Murine macrophage C- type lectin [Mus musculus] g5821286	BLAST-GenBank MOTIFS SPSCAN HMMER HMMER-PFAM BLIMPS-BLOCKS PROFILES-SCAN BLAST-DOMO
4	276	S213 S91 S113 S35 S70 S76 S147 T163 S206		Signal peptide: M1-G31 Transmembrane domain: I184-F201 Cell attachment sequence: R149-D151		BLAST-GenBank MOTIFS HMMER

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosyla- tion Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
5	375	S18 S205 T286 S3 S120 S197 T260 Y85		Transmembrane domains: W139-R158; F173-H191 P232-Q254 Transmembrane protein signature: I95-C369	Transmembrane protein [S. pombe] g1065898	BLAST-GenBank MOTIFS HMMER BLAST-DOMO BLAST-PRODOM
6	249	T7 T135 T170 S204 Y154	N18 N92 N147		Phospholipid scramblase [Homo sapiens] g4092081	BLAST-GenBank MOTIFS
7	353	T162 T4 S97 T115 S165 S194 T225 S242 S17 S47 S205	N299	Signal peptide: M1-A33	Paraneoplastic neuronal antigen MA1 [Homo sapiens] g4104634	BLAST-GenBank MOTIFS SPSCAN
8	194	T12 S115 S29 S99 S187	N95 N147	Signal peptide: M1-C50 Transmembrane domain: L38-L56 C-type lectin domain: C75-E194	Lectin-like NK cell receptor LIT1 [Homo sapiens] g6651065	BLAST-GenBank MOTIFS SPSCAN HMMER HMMER-PFAM BLIMPS-BLOCKS BLAST-DOMO
9	322	S304 S48 S146 S72 T133 S255 S280	N20 N60 N70	Signal peptide: M1-A50		BLAST-GenBank MOTIFS SPSCAN

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosyla- tion Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
10	335	S125 S140 S183 S222 T252		Transmembrane domains: G71-L94; A255-I283 GufA transmembrane protein domain: L12-H101; G180-G335 Glycosaminoglycan attachment site: S310-G313	GufA protein [Thermotoga maritima] g4982315	BLAST-GenBank MOTIFS HMMER BLAST-PRODOM BLAST-DOMO
11	620	S49 S108 T146 S300 T348 T349 S607 S4 S128 S183 S234 T420 S460 S467 S543 Y597	N144 N202 N264 N274 N293 N341 N492 N505 N526 N542	Transmembrane domain: M563-W582 Immunoglobulin domain: G439-A499 Leucine-rich repeat signature: L337-L350 Glycoprotein hormone receptor domain: T40-L198	Slit2 [Rattus norvegicus] g4585574	BLAST-GenBank MOTIFS HMMER HMMER-PFAM BLIMPS-PRINTS BLAST-DOMO

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosyla- tion Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
12	491	T231 T232 S253 T482 S185 S276	N56 N220 N229	Transmembrane domains: I115-I142; I184-V201 F422-F441 Transmembrane protein domain: L8-Y215; I396-F471	Selectively expressed in embryonic epithelia protein-1 [Mus musculus] g6715148 PB39 [Homo sapiens] g3462515	BLAST-GenBank MOTIFS HMMER BLAST-PRODOM
13	580	S557 S10 T34 S51 T92 T210 S343 T12 S217 T222 S268 S296 T417 T523 S550	N159 N179 N220 N230	Transmembrane domains: F297-F313; I356-I373 L496-I514 Lipases serine active site: L104-A113		MOTIFS HMMER
14	455	T53 T182 S239 S69 S135 S202 T280 S355 S372 Y38	N67 N180 N243	Transmembrane domains: V81-V99; I343-I361 S375-V392; W425-Y442 Glycosaminoglycan attachment site: S162-G165	putative G- protein coupled receptor [Homo sapiens] g6649579	BLAST-GenBank MOTIFS HMMER

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosyla- tion Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
15	277	S265 T66 T225 S268 S273 S30 S49 S61 S152 S193 Y242	N29 N38 N47 N48 N92 N160 N210	Transmembrane domain: K9-F27 Brush border protein domain: Y8-R277 RGD cell attachment sequence: R113-D115	AdRab-A brush border membrane protein [Oryctolagus cuniculus] gl762	BLAST-GenBank MOTIFS HMMER BLAST-PRODOM
16	647	S490 T50 S67 S105 T110 S121 T220 S249 S264 S272 S322 T389 S469 T501 S639 S132 T155 S242 S324 T381 T400 S522 S554	N261	Signal peptide: M1-A22 Transmembrane domains: L328-L347; M406-L424 L559-A578; W618-L638 GufA transmembrane protein domain: E485-L640 Glycosaminoglycan attachment site: S34-G37	LIV-1 protein [Homo sapiens] gl256001	BLAST-GenBank MOTIFS SPSCAN HMMER BLAST-PRODOM
17	406	S29 S215 S236 T69	N23	Transmembrane domains: Q76-V95; W286-S313 M367-I384		MOTIFS HMMER

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosyla- tion Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
18	290	T221 S44 S69 S71 S81 T94 T101 T113 T131 S216 Y284	N88	Signal peptide: M1-A19 Transmembrane domains: P160-M181 Immunoglobulin domain: R33-I110 Transmembrane glycoprotein domain: I22-D116	NK inhibitory receptor [Homo sapiens] g6707799 CMRF-35-H9 leukocyte antigen [Homo sapiens] g4103066	BLAST-GenBank MOTIFS SPSCAN HMMER HMMER-PFAM BLAST-PRODOM BLAST-DOMO
19	390	S7 T68 S153 T23 T166 T281 Y20 Y37	N5 N88 N330 N367	Immunoglobulins and MHC proteins signature: T90-P112; F242-V259 Glycoprotein antigen signature: L61-V72; V92-I113		MOTIFS BLIMPS-BLOCKS BLIMPS-PRODOR
20	427	S13 S41 S65 S66 S99 T150 S323 S324 S101 S275 S353 S367 T399 Y71	N106 N148 N171 N233 N312	Mucin glycoprotein precursor domain: V136-P142	Gastric mucin [Sus scrofa] g915208	BLAST-GenBank MOTIFS BLIMPS-PRODOR

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosyla- tion Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
21	459	T4 S60 S66 S116 T176 S16 T235	N14 N158 N323	Transmembrane domains: F202-V219; I246-L268 W343-L367; P417-P440	six transmembrane epithelial antigen of prostate [Homo sapiens] g6572948	BLAST-GenBank MOTIFS HMMER
22	229	S13 S118 T155 Y24		Transmembrane domains: I93-V111; V132-L150 F164-V182 Transmembrane protein domain: S156-V182		MOTIFS HMMER BLIMPS-PRODOM
23	311	S85 S234 S236 S269 S80 S119 S186 T294	N22	Transmembrane domains: W58-I76; P152-K177 A216-Y232		MOTIFS HMMER
24	92	S47 T54 T12 S70	N62		HERV-E envelope glycoprotein [Homo sapiens] g2587024	BLAST-GenBank MOTIFS
25	258	S34 T33 S148 S243		Transmembrane domains: I39-I57; F86-L106 V122-I140; L190-S210		MOTIFS HMMER

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosyla- tion Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
26	226	S56 S128 T196 T167 Y194	N54 N187 N198	Signal peptide: M1-P50 Transmembrane domains: T23-L43; M72-A89 I101-I124; I158-N178 Transmembrane 4 family signature: A70-I120 Lysosomal-associated transmembrane protein domain: C15-Y223	MTP (mouse transporter protein) [Mus musculus] g1276631	BLAST-GenBank MOTIFS SPSCAN HMMER PROFILESKAN BLAST-PRODOM
27	136	S3 S132		Signal peptide: M1-R53 Transmembrane domains: I10-L28; T26-I50 F70-L89 Transmembrane protein domain: D31-V104		MOTIFS SPSCAN HMMER BLAST-PRODOM

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosyla- tion Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
28	458	T408 T98 S126 S170 T334	N96 N151 N293 N332	Signal peptide: M1-A20 Transmembrane domain: L10-N30 Membrane glycoprotein signature: L9-V101; L64-Q457 Olfactory ligand binding domain: T67-S452	Potential ligand (odorant) binding protein [Rattus rattus] g57732	BLAST-GenBank MOTIFS SPSCAN HMMER BLAST-PRODOM BLAST-DOMO
29	368	S24 T166 T302 S12 S134 Y307	N17		Fuzzy (TM protein involved in tissue polarity) [Drosophila melanogaster] g2564657	BLAST-GenBank MOTIFS
30	91	T44 S84		Signal peptide: M1-A19 Transmembrane domain: P58-S82 Glycophorin A proteins signature: T22-S32; I63-G91 Glycophorin domain: M1-R86	Preglycophorin B [Homo sapiens] g4803699	BLAST-GenBank MOTIFS SPSCAN HMMER BLIMPS-BLOCKS PROFILESCAN BLAST-PRODOM BLAST-DOMO

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosyla- tion Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
31	295	S96 T113 S129 T155 T125 T157 T187 S222 T231 T263 Y212	N111 N169 N223	Signal peptide: M1-G48 Transmembrane domain: L241-L259 Immunoglobulin domain: K159-V216 Carcinoembryonic antigen domain: I38-P147 Glycoprotein antigen domain: M1-V140; Y141-Y234 G239-S295	Biliary glycoprotein [Mus musculus] g312590	BLAST-GenBank MOTIFS SPSCAN HMMER HMMER-PFAM BLAST-PRODOM BLAST-DOMO
32	724	T39 S47 T171 S205 T224 S225 T241 S285 S301 T323 S352 T353 S439 S509 S517 S537 T659 T707 S8 S18 S49 S72 T85 T159 S173 S271 S367 S560 S588 Y499	N279 N348	Transmembrane domain: I611-F630 Membrane protein domain: T4-L209		MOTIFS HMMER BLAST-DOMO

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosyla- tion Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
33	331	S117 S147 S149 T320 S138 S174 T274 T319 S328 Y198	N222	Signal peptide: M1-S16 Transmembrane domains: A67-N87; I118-C134 W240-V269; L294-Y310 Transmembrane protein domain: A6-T311	Putative Golgi UDP-GlcNAC transporter [S. pombe] g3738167	BLAST-GenBank MOTIFS SPSCAN HMMER BLAST-PRODOM
34	398	T42 T158 S271 S28 S285 T334 S375		Transmembrane domain: I59-L79 Band 7 family domain: F64-A231, A78-V90; R116-L154 Stomatin signature: T84-L106; L131-P152 T166-L183; I186-G209 L54-Q227	Stomatin-like protein UNC24 [Homo sapiens] g5326747	BLAST-GenBank MOTIFS HMMER HMMER-PFAM BLIMPS-BLOCKS BLIMPS-PRINTS BLAST-PRODOM BLAST-DOMO
35	220	S199 T120 S192	N107	Signal peptide: M1-G19 Leucine rich repeats: A62-F85; Q86-S109 G110-G133; A134-R157 A158-S181; H184-P207	Similar to Leucine-rich transmembrane proteins [Homo sapiens] g2781386	BLAST-GenBank MOTIFS SPSCAN HMMER HMMER-PFAM BLIMPS-PRINTS

Table 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosyla- tion Sites	Signature Sequences, Motifs, and Domains	Homologous Sequences	Analytical Methods and Databases
36	706	T564 T74 T113 S291 S452 S632 S14 T42 S66 T115 T142 S286 T551 T575 S701	N101	Transmembrane domains: F158-M178; L344-V368 L425-L442; M478-F498 A581-I604; L641-V665 Glycosaminoglycan attachment site: S223-G226	LAK-4p [Homo sapiens] g7209574	BLAST-GenBank MOTIFS HMMER
37	466	T326 S10 T46 T105 S187 S98 T164 T310 S321 Y388	N368	Signal peptide: M1-G23 Transmembrane domain: A236-I255 SPRY domain: A338-S464; E123-S136 E322-W343; V407-F420 Butyrophilin domain: W19-C114	Butyrophilin like receptor [Homo sapiens] g4587209	BLAST-GenBank MOTIFS SPSCAN HMMER HMMER-PFAM BLIMPS-PFAM BLAST-PRODOM BLAST-DOMO

Table 3

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
38	844-888	Nervous (0.377) Reproductive (0.180) Cardiovascular (0.115) Gastrointestinal (0.115)	Cancer (0.410) Inflammation/Trauma (0.296) Cell Proliferation (0.131)	PBLUESCRIPT
39	579-623	Developmental (0.400) Musculoskeletal (0.200) Nervous (0.200) Urologic (0.200)	Cancer (0.400) Cell Proliferation (0.400)	PSPORT1
40	336-380	Cardiovascular (0.267) Hematopoietic/Immune (0.200) Endocrine (0.133) Reproductive (0.133)	Cancer (0.400) Inflammation/Trauma (0.400) Cell Proliferation (0.133)	pINCY
41	596-640	Nervous (0.588) Gastrointestinal (0.118) Reproductive (0.118)	Inflammation/Trauma (0.470) Cancer (0.235) Cell Proliferation (0.176)	pINCY
42	1281-1325	Reproductive (0.237) Hematopoietic/Immune (0.145) Nervous (0.145)	Cancer (0.441) Inflammation/Trauma (0.323) Cell Proliferation (0.178)	pINCY
43	227-271	Reproductive (0.444) Dermatologic (0.222) Endocrine (0.111) Gastrointestinal (0.111) Nervous (0.111)	Cancer (0.333) Cell Proliferation (0.222) Inflammation/Trauma (0.222)	pINCY

Table 3

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
44	1368-1412	Nervous (0.339) Reproductive (0.278) Gastrointestinal (0.104)	Cancer (0.478) Inflammation/Trauma (0.278) Cell Proliferation (0.165)	pINCY
45	543-587	Hematopoietic/Immune (0.500) Gastrointestinal (0.188)	Inflammation/Trauma (0.500) Cancer (0.250) Cell Proliferation (0.188)	pINCY
46	280-324	Reproductive (0.267) Nervous (0.233) Gastrointestinal (0.112)	Cancer (0.483) Inflammation/Trauma (0.345) Cell Proliferation (0.155)	pINCY
47	380-424 875-919	Reproductive (0.412) Gastrointestinal (0.176) Cardiovascular (0.118)	Cancer (0.647) Inflammation/Trauma (0.178)	PSPORT1
48	272-316 1514-1558	Nervous (0.645) Developmental (0.129)	Cancer (0.355) Cell Proliferation (0.258) Neurological (0.194)	PSPORT1
49	282-326 768-812	Hematopoietic/Immune (0.238) Gastrointestinal (0.155) Reproductive (0.143)	Cancer (0.381) Inflammation/Trauma (0.381) Cell Proliferation (0.202)	PSPORT1
50	597-641 1074-1118	Reproductive (0.214) Nervous (0.196) Hematopoietic/Immune (0.143)	Cancer (0.464) Inflammation/Trauma (0.304) Cell Proliferation (0.196)	PSPORT1
51	973-1017	Reproductive (0.266) Nervous (0.234) Hematopoietic/Immune (0.125)	Cancer (0.516) Inflammation/Trauma (0.359) Cell Proliferation (0.109)	PSPORT1

Table 3

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
52	299-343	Gastrointestinal (1.000)	Cancer (0.500) Inflammation/Trauma (0.500)	pINCY
53	380-424 1199-1243	Gastrointestinal (0.289) Reproductive (0.244) Cardiovascular (0.111) Hematopoietic/Immune (0.111)	Cancer (0.578) Inflammation/Trauma (0.311) Cell Proliferation (0.178)	pINCY
54	1135-1179	Nervous (0.195) Reproductive (0.186) Gastrointestinal (0.144)	Cancer (0.449) Inflammation/Trauma (0.305) Cell Proliferation (0.144)	pINCY
55	325-369 820-864	Hematopoietic/Immune (0.750)	Inflammation/Trauma (0.625) Cancer (0.125)	pINCY
56	487-531 1090-1134	Nervous (0.583)	Cancer (0.458) Inflammation/Trauma (0.250)	pINCY
57	569-613 1360-1405	Reproductive (0.429) Hematopoietic/Immune (0.286) Musculoskeletal (0.143) Urologic (0.143)	Cancer (0.571) Inflammation/Trauma (0.286) Cell Proliferation (0.143)	pINCY
58	272-472 551-595 812-1012 1523-1567	Reproductive (0.350) Nervous (0.150) Cardiovascular (0.100) Gastrointestinal (0.100) Hematopoietic/Immune (0.100) Urologic (0.100)	Cancer (0.500) Inflammation/Trauma (0.500)	pINCY

Table 3

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
59	217-261	Nervous (0.286) Developmental (0.143) Gastrointestinal (0.143) Hematopoietic/Immune (0.143) Reproductive (0.143)	Inflammation/Trauma (0.428) Cancer (0.357) Cell Proliferation (0.143)	PBLUESCRIPT
60	444-488	Nervous (0.207) Reproductive (0.207) Gastrointestinal (0.130) Hematopoietic/Immune (0.130)	Cancer (0.467) Inflammation/Trauma (0.359) Cell Proliferation (0.163)	PSPORT1
61	643-687	Reproductive (0.464) Endocrine (0.143) Cardiovascular (0.107) Gastrointestinal (0.107)	Cancer (0.500) Inflammation/Trauma (0.321)	PSPORT1
62	146-344 390-434 506-704 786-830	Gastrointestinal (0.500) Hematopoietic/Immune (0.250) Reproductive (0.250)	Cancer (0.750) Inflammation/Trauma (0.250)	pINCY
63	163-207	Reproductive (0.315) Gastrointestinal (0.161) Cardiovascular (0.147)	Cancer (0.594) Cell Proliferation (0.231) Inflammation/Trauma (0.210)	pINCY
64	201-506 525-569 606-912 975-1280 1362-1406	Gastrointestinal (0.455) Cardiovascular (0.273) Reproductive (0.189)	Cancer (0.455) Inflammation/Trauma (0.367) Cell Proliferation (0.189)	PSPORT1

Table 3

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
65	703-747	Gastrointestinal (0.667) Cardiovascular (0.167) Reproductive (0.167)	Cancer (1.000)	pINCY
66	271-315 319-363	Nervous (0.314) Reproductive (0.314) Developmental (0.114) Urologic (0.114)	Cancer (0.429) Cell Proliferation (0.171) Inflammation/Trauma (0.143)	pINCY
67	319-363	Developmental (0.364) Hematopoietic/Immune (0.364) Gastrointestinal (0.182)	Cell Proliferation (0.727) Cancer (0.273) Inflammation/Trauma (0.182)	pINCY
68	812-856	Reproductive (0.444) Nervous (0.222) Endocrine (0.111) Hematopoietic/Immune (0.111) Musculoskeletal (0.111)	Cancer (0.556) Inflammation/Trauma (0.333)	pINCY
69	596-640 1577-1621	Reproductive (0.255) Nervous (0.184) Developmental (0.122) Gastrointestinal (0.122)	Cancer (0.429) Inflammation/Trauma (0.337) Cell Proliferation (0.255)	pINCY
70	379-675 703-747 766-1062 1081-1347	Nervous (0.467) Hematopoietic/Immune (0.200) Reproductive (0.133) Urologic (0.133)	Cancer (0.467) Cell Proliferation (0.267) Inflammation/Trauma (0.267)	pINCY

Table 3

Nucleotide SEQ ID NO:	Selected Fragments	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
71	18-62	Nervous (0.265) Reproductive (0.206) Musculoskeletal (0.147)	Cancer (0.500) Inflammation/Trauma (0.264) Cell Proliferation (0.147)	pINCY
72	290-488 507-704 759-803	Gastrointestinal (0.333) Hematopoietic/Immune (0.333) Nervous (0.333)	Inflammation/Trauma (0.667) Cancer (0.333)	pINCY
73	649-693 1711-1755	Reproductive (0.392) Gastrointestinal (0.294) Cardiovascular (0.118)	Cancer (0.686) Inflammation/Trauma (0.294)	pINCY
74	704-748	Gastrointestinal (0.923)	Cancer (0.462) Inflammation/Trauma (0.385)	pINCY

Table 4

Nucleotide SEQ ID NO:	Library	Library Description
38	PITUNOT01	This library was constructed using RNA obtained from Clontech (CLON 6584-2, lot 35278). The RNA was isolated from pituitary glands removed from a pool of 18 male and female Caucasian donors, 16 to 70 years old, who died from trauma.
39	KIDNTUT01	This library was constructed using RNA isolated from kidney tumor tissue removed from an 8-month-old female during nephroureterectomy. Pathology indicated Wilms' tumor (nephroblastoma), which involved 90 percent of the renal parenchyma. Prior to surgery, the patient was receiving heparin anticoagulant therapy.
40	BLADTUT04	This library was constructed using RNA isolated from bladder tumor tissue removed from a 60-year-old Caucasian male during a radical cystectomy, prostatectomy, and vasectomy. Pathology indicated grade 3 transitional cell carcinoma in the left bladder wall. Carcinoma in-situ was identified in the dome and trigone. Patient history included tobacco use. Family history included type I diabetes, malignant neoplasm of the stomach, atherosclerotic coronary artery disease, and acute myocardial infarction.
41	PROSNOT19	This library was constructed using RNA isolated from diseased prostate tissue removed from a 59-year-old Caucasian male during a radical prostatectomy with regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 3+3). The patient presented with elevated prostate-specific antigen (PSA). Patient history included colon diverticuli, asbestosis, and thrombophlebitis. Family history included benign hypertension, multiple myeloma, hyperlipidemia and rheumatoid arthritis.
42	ISLTNUT01	This library was constructed using RNA isolated from a pooled collection of pancreatic islet cells.

Table 4

Nucleotide SEQ ID NO:	Library	Library Description
43	ENDCNOT03	This library was constructed using RNA isolated from dermal microvascular endothelial cells removed from a neonatal Caucasian male.
44	SMCANOT01	This library was constructed using RNA isolated from an aortic smooth muscle cell line derived from the explanted heart of a male obtained during a heart transplant.
45	THYMNOT04	This library was constructed using RNA isolated from thymus tissue removed from a 3-year-old Caucasian male, who died from anoxia.
46	FTBAUNT02	This library was constructed using RNA isolated from untreated aortic adventitial fibroblasts removed from a 65-year-old Caucasian female.
47	BRSTTUT01	This library was constructed using RNA isolated from breast tumor tissue removed from a 55-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated invasive grade 4 mammary adenocarcinoma. Patient history included atrial tachycardia and a benign breast neoplasm. Family history included cardiovascular and cerebrovascular disease and depressive disorder.
48	BRAITUT01	This library was constructed using RNA isolated from brain tumor tissue removed from a 50-year-old Caucasian female during a frontal lobectomy. Pathology indicated recurrent grade 3 oligoastrocytoma with focal necrosis and extensive calcification. Patient history included a speech disturbance and epilepsy. The patient's brain had also been irradiated with a total dose of 5,082 cGy (Fraction 8). Family history included a brain tumor.
49	RATRNUT02	This library was constructed using RNA isolated from the right atrium tissue of a 39-year-old Caucasian male, who died from a gunshot wound.

Table 4

Nucleotide SEQ ID NO:	Library	Library Description
50	BRSTNOT02	This library was constructed using RNA isolated from diseased breast tissue removed from a 55-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated proliferative fibrocystic changes characterized by apocrine metaplasia, sclerosing adenosis, cyst formation, and ductal hyperplasia without atypia. Pathology for the associated tumor tissue indicated an invasive grade 4 mammary adenocarcinoma. Patient history included atrial tachycardia and a benign neoplasm. Family history included cardiovascular and cerebrovascular disease.
51	BRSTNOT03	This library was constructed using RNA isolated from diseased breast tissue removed from a 54-year-old Caucasian female during a bilateral radical mastectomy. Pathology for the associated tumor tissue indicated residual invasive grade 3 mammary ductal adenocarcinoma. Patient history included kidney infection and condyloma acuminatum. Family history included benign hypertension, hyperlipidemia and a malignant neoplasm of the colon.
52	COLNNOT13	This library was constructed using RNA isolated from ascending colon tissue of a 28-year-old Caucasian male with moderate chronic ulcerative colitis.
53	COLNNOT13	This library was constructed using RNA isolated from ascending colon tissue of a 28-year-old Caucasian male with moderate chronic ulcerative colitis.
54	PENITUT01	This library was constructed using RNA isolated from tumor tissue removed from the penis of a 64-year-old Caucasian male during penile amputation. Pathology indicated a fungating invasive grade 4 squamous cell carcinoma involving the inner wall of the foreskin and extending onto the glans penis. Patient history included benign neoplasm of the large bowel, atherosclerotic coronary artery disease, angina pectoris, gout, and obesity. Family history included malignant pharyngeal neoplasm, chronic lymphocytic leukemia, and chronic liver disease.

Table 4

Nucleotide SEQ ID NO:	Library	Library Description
55	SPLNNOT04	This library was constructed using RNA isolated from the spleen tissue of a 2-year-old Hispanic male, who died from cerebral anoxia.
56	BRAITUT12	This library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe of a 40-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology indicated grade 4 gemistocytic astrocytoma.
57	URETTUT01	This library was constructed using RNA isolated from right ureter tumor tissue of a 69-year-old Caucasian male during ureterectomy and lymph node excision. Pathology indicated invasive grade 3 transitional cell carcinoma. Patient history included benign colon neoplasm, tobacco use, asthma, emphysema, acute duodenal ulcer, and hyperplasia of the prostate. Family history included atherosclerotic coronary artery disease, congestive heart failure, and malignant lung neoplasm.
58	PROSNOT18	This library was constructed using RNA isolated from diseased prostate tissue removed from a 58-year-old Caucasian male during a radical cystectomy, radical prostatectomy, and gastrectomy. Pathology indicated adenofibromatous hyperplasia; this tissue was associated with a grade 3 transitional cell carcinoma. Patient history included angina and emphysema. Family history included acute myocardial infarction, atherosclerotic coronary artery disease, and type II diabetes.
59	PITUNOT01	This library was constructed using RNA obtained from Clontech (CLON 6584-2, lot 35278). The RNA was isolated from the pituitary glands removed from a pool of 18 male and female Caucasian donors, 16 to 70 years old, who died from trauma.

Table 4

Nucleotide SEQ ID NO:	Library	Library Description
60	BRSTTUT03	This library was constructed using RNA isolated from breast tumor tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated multicentric invasive grade 4 lobular carcinoma. The mass was identified in the upper outer quadrant, and three separate nodules were found in the lower outer quadrant of the left breast. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular disease, coronary artery aneurysm, breast cancer, prostate cancer, atherosclerotic coronary artery disease, and type I diabetes.
61	OVARNOT03	This library was constructed using RNA isolated from ovarian tissue removed from a 43-year-old Caucasian female during removal of the fallopian tubes and ovaries. Pathology for the associated tumor tissue indicated grade 2 mucinous cystadenocarcinoma. Patient history included mitral valve disorder, pneumonia, and viral hepatitis. Family history included atherosclerotic coronary artery disease, pancreatic cancer, stress reaction, cerebrovascular disease, breast cancer, and uterine cancer.
62	TESTTUT02	This library was constructed using RNA isolated from testicular tumor tissue removed from a 31-year-old Caucasian male during unilateral orchiectomy. Pathology indicated embryonal carcinoma.
63	NPOLNOT01	This library was constructed using RNA isolated from nasal polyp tissue removed from a 78-year-old Caucasian male during a nasal polypectomy. Pathology indicated a nasal polyp and striking eosinophilia. Patient history included asthma and nasal polyps.

Table 4

Nucleotide SEQ ID NO:	Library	Library Description
64	OVARTUN01	This normalized library was constructed from 5.36 million independent clones obtained from an ovarian tumor library. RNA was isolated from tumor tissue removed from the left ovary of a 58-year-old Caucasian female during a total abdominal hysterectomy, removal of a single ovary, and inguinal hernia repair. Pathology indicated a metastatic grade 3 adenocarcinoma of colonic origin, forming a partially cystic and necrotic tumor mass in the left ovary, and a nodule in the left mesovarium. A single intramural leiomyoma was identified in the myometrium. The cervix showed mild chronic cystic cervicitis. Patient history included benign hypertension, follicular ovarian cyst, colon cancer, benign colon neoplasm, and osteoarthritis. Family history included emphysema, myocardial infarction, atherosclerotic coronary artery disease, benign hypertension, hyperlipidemia, and primary tuberculous complex. The normalization and hybridization conditions were adapted from Soares et al. (PNAS (1994) 91:9228) and Bonaldo et al. (Genome Research (1996) 6:791).
65	LUNGNOT28	This library was constructed using RNA isolated from lung tissue removed from a 53-year-old male. Pathology for the associated tumor tissue indicated grade 4 adenocarcinoma.
66	EPIGNOT01	This library was constructed using RNA isolated from epiglottic tissue removed from a 71-year-old male during laryngectomy with right parathyroid biopsy. Pathology for the associated tumor tissue indicated recurrent grade 1 papillary thyroid carcinoma.
67	LIVRNOT03	This library was constructed using RNA isolated from liver tissue removed from a Caucasian male fetus, who died from Patau's syndrome (trisomy 13) at 20 weeks' gestation.

Table 4

Nucleotide SEQ ID NO:	Library	Library Description
68	CONFNOT03	This library was constructed using RNA isolated from mesenteric fat tissue removed from a 71-year-old Caucasian male during a partial colectomy and permanent colostomy. Pathology indicated mesenteric fat tissue associated with diverticulosis and diverticulitis with abscess formation. Approximately 50 diverticula were noted, one of which was perforated and associated with abscess formation in adjacent mesenteric fat. The patient presented with atrial fibrillation. Patient history included viral hepatitis, a hemangioma, and diverticulitis of colon. Family history included extrinsic asthma, atherosclerotic coronary artery disease, and myocardial infarction.
69	COLSTUT01	This library was constructed using RNA isolated from colon tumor tissue removed from the sigmoid colon of a 62-year-old Caucasian male during a sigmoidectomy and permanent colostomy. Pathology indicated invasive grade 2 adenocarcinoma, with invasion through the muscularis. Patient history included hyperlipidemia, cataract disorder and dermatitis. Family history included benign hypertension, atherosclerotic coronary artery disease, hyperlipidemia, breast cancer, and prostate cancer.
70	BRSTNOT33	This library was constructed using RNA isolated from right breast tissue removed from a 46-year-old Caucasian female during a unilateral extended simple mastectomy with breast reconstruction. Pathology for the associated tumor tissue indicated invasive grade 3 adenocarcinoma, ductal type, with apocrine features, nuclear grade 3 forming a mass in the outer quadrant. There was greater than 50% intraductal component. Patient history included breast cancer.

Table 4

Nucleotide SEQ ID NO:	Library	Library Description
71	BRAINOT22	This library was constructed using RNA isolated from right temporal lobe tissue removed from a 45-year-old Black male during a brain lobectomy. Pathology for the associated tumor tissue indicated dysembryoplastic neuroepithelial tumor of the right temporal lobe. The right temporal region dura was consistent with calcifying pseudotumor of the neuraxis. Patient history included obesity, meningitis, backache, unspecified sleep apnea, acute stress reaction, acquired knee deformity, and chronic sinusitis. Family history included obesity, benign hypertension, cirrhosis of the liver, obesity, hyperlipidemia, cerebrovascular disease, and type II diabetes.
72	LIVRDIR01	This library was constructed using RNA isolated from diseased liver tissue removed from a 63-year-old Caucasian female during a liver transplant. Patient history included primary biliary cirrhosis. Serology was positive for anti-mitochondrial antibody.
73	COLADIT05	This library was constructed using RNA isolated from diseased ascending colon tissue removed from a 32-year-old Caucasian male during a total intra-abdominal colectomy, abdominal-perineal rectal resection, and temporary ileostomy. Pathology indicated chronic ulcerative colitis extending in a continuous fashion from the mid-portion of the ascending colon distally to the rectum. This was characterized microscopically by crypt abscess formation and inflammation confined to the mucosa and submucosa. The terminal ileum exhibited ileitis and the rectal mucosa showed crypt abscess formation. Patient history included tobacco use. Family history included ulcerative colitis, malignant neoplasm of the breast and acute myocardial infarction.

Table 4

Nucleotide SEQ ID NO:	Library	Library Description
74	SINITMT04	<p>Library was constructed using RNA isolated from ileum tissue removed from a 70-year-old Caucasian female during right hemicolectomy, open liver biopsy, flexible sigmoidoscopy, colonoscopy, and permanent colostomy. Pathology indicated a non-tumorous margin of ileum. Pathology for the associated tumor indicated invasive grade 2 adenocarcinoma forming an ulcerated mass, situated 2 cm distal to the ileocecal valve. The tumor invaded through the muscularis propria just into the serosal adipose tissue. One (of 16) regional lymph node was positive for a microfocus of metastatic adenocarcinoma. Patient history included a malignant breast neoplasm, type II diabetes, hyperlipidemia, viral hepatitis, an unspecified thyroid disorder, osteoarthritis, and a malignant skin neoplasm. Family history included breast cancer, atherosclerotic coronary artery disease, benign hypertension, cerebrovascular disease, ovarian cancer, and hyperlipidemia.</p>

Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	PE Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	PE Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	PE Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25:3389-3402.	ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises at least five functions: fasta, ifasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad. Sci. USA 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183:63-98; and Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489.	ESTs: fasta E value=1.0E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less Full Length sequences: fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S. and J.G. Henikoff (1991) Nucleic Acids Res. 19:6565-6572; Henikoff, J.G. and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37:417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and, if applicable, Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol. 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

Table 5 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, M. et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221.	Normalized quality score \geq GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M.S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies.	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12:431-439.	Score=3.5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

5 a) an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37,

b) a naturally occurring amino acid sequence having at least 70% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37,

20 c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, and

d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37.

35 2. An isolated polypeptide of claim 1 selected from the group consisting of SEQ ID NO:1,

SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37.

3. An isolated polynucleotide encoding a polypeptide of claim 1.

10 4. An isolated polynucleotide encoding a polypeptide of claim 2.

5. An isolated polynucleotide of claim 4 selected from the group consisting of SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74.

20 6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.

7. A cell transformed with a recombinant polynucleotide of claim 6.

25 8. A transgenic organism comprising a recombinant polynucleotide of claim 6.

9. A method for producing a polypeptide of claim 1, the method comprising:

a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1, and

b) recovering the polypeptide so expressed.

10. An isolated antibody which specifically binds to a polypeptide of claim 1.

35

11. An isolated polynucleotide comprising a polynucleotide sequence selected from the group consisting of:

- a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74,
- b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74,
- c) a polynucleotide sequence complementary to a),
- d) a polynucleotide sequence complementary to b), and
- e) an RNA equivalent of a)-d).

12. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 11.

13. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

- a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and
- b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

14. A method of claim 13, wherein the probe comprises at least 60 contiguous nucleotides.

15. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 11, the method comprising:

a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and

5 b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

16. A composition comprising an effective amount of a polypeptide of claim 1 and a pharmaceutically acceptable excipient.

10

17. A composition of claim 16, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37.

15

18. A method for treating a disease or condition associated with decreased expression of functional MEMAP, comprising administering to a patient in need of such treatment the composition of claim 16.

20

19. A method for screening a compound for effectiveness as an agonist of a polypeptide of claim 1, the method comprising:

25 a) exposing a sample comprising a polypeptide of claim 1 to a compound, and

b) detecting agonist activity in the sample.

20. A composition comprising an agonist compound identified by a method of claim 19 and a pharmaceutically acceptable excipient.

30

21. A method for treating a disease or condition associated with decreased expression of functional MEMAP, comprising administering to a patient in need of such treatment a composition of claim 20.

35

22. A method for screening a compound for effectiveness as an antagonist of a polypeptide

of claim 1, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting antagonist activity in the sample.

5 23. A composition comprising an antagonist compound identified by a method of claim 22 and a pharmaceutically acceptable excipient.

 24. A method for treating a disease or condition associated with overexpression of functional MEMAP, comprising administering to a patient in need of such treatment a composition of claim 23.
10

 25. A method of screening for a compound that specifically binds to the polypeptide of claim 1, said method comprising the steps of:

- a) combining the polypeptide of claim 1 with at least one test compound under suitable conditions, and
- 15 b) detecting binding of the polypeptide of claim 1 to the test compound, thereby identifying a compound that specifically binds to the polypeptide of claim 1.

 26. A method of screening for a compound that modulates the activity of the polypeptide of claim 1, said method comprising:

- 20 a) combining the polypeptide of claim 1 with at least one test compound under conditions permissive for the activity of the polypeptide of claim 1,
- b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound, and
- c) comparing the activity of the polypeptide of claim 1 in the presence of the test compound
- 25 with the activity of the polypeptide of claim 1 in the absence of the test compound, wherein a change in the activity of the polypeptide of claim 1 in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide of claim 1.

 27. A method for screening a compound for effectiveness in altering expression of a target
30 polynucleotide, wherein said target polynucleotide comprises a sequence of claim 5, the method comprising:

- a) exposing a sample comprising the target polynucleotide to a compound, and
- b) detecting altered expression of the target polynucleotide.

35 28. A method for assessing toxicity of a test compound, said method comprising:

- a) treating a biological sample containing nucleic acids with the test compound;
- b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide of claim 11 under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim 11 or fragment thereof;
- c) quantifying the amount of hybridization complex; and
- d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

SEQUENCE LISTING

<110> INCYTE GENOMICS, INC.

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YUE, Henry

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BANDMAN, Olga

BURFORD, Neil

AZIMZAI, Yalda

BAUGHN, Mariah R.

LU, Dyung Aina M.

PATTERSON, Chandra

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Ile Val Trp Gly Pro	Thr Val Ser Arg	Glu Asp Gly Gly Asp Pro	
	110	115	120
Asn Ser Ala Asn Pro	Gly Phe Leu Asp	Tyr Gly Phe Ala Ala Pro	
	125	130	135
His Gly Leu Ala Thr	Pro His Pro Asn	Ser Asp Ser Met Arg Gly	
	140	145	150
Asp Gly Asp Gly Leu	Ile Leu Gly Glu	Ala Pro Ala Thr Leu Arg	
	155	160	165
Pro Phe Leu Phe Gly	Gly Arg Gly Glu	Gly Val Asp Pro Gln Leu	
	170	175	180
Tyr Val Thr Ile Thr	Ile Ser Ile Ile	Ile Val Leu Val Ala Thr	
	185	190	195
Gly Ile Ile Phe Lys	Phe Cys Trp Asp	Arg Ser Gln Lys Arg Arg	
	200	205	210
Arg Pro Ser Gly Gln	Gln Gly Ala Leu	Arg Gln Glu Glu Ser Gln	
	215	220	225
Gln Pro Leu Thr Asp	Leu Ser Pro Ala	Gly Val Thr Val Leu Gly	
	230	235	240
Ala Phe Gly Asp Ser	Pro Thr Pro Thr	Pro Asp His Glu Glu Pro	
	245	250	255
Arg Gly Gly Pro Arg	Pro Gly Met Pro	His Pro Lys Gly Ala Pro	
	260	265	270
Ala Phe Gln Leu Asn	Arg		
	275		

<210> 5

<211> 375

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2071941CD1

<400> 5

Met	Ser	Ser	His	Lys	Gly	Ser	Val	Val	Ala	Gln	Gly	Asn	Gly	Ala	
1				5					10					15	
Pro	Ala	Ser	Asn	Arg	Glu	Ala	Asp	Thr	Val	Glu	Leu	Ala	Glu	Leu	
				20					25					30	
Gly	Pro	Leu	Leu	Glu	Glu	Lys	Gly	Lys	Arg	Val	Ile	Ala	Asn	Pro	
				35					40					45	
Pro	Lys	Ala	Glu	Glu	Glu	Gln	Thr	Cys	Pro	Val	Pro	Gln	Glu	Glu	
				50					55					60	
Glu	Glu	Glu	Val	Arg	Val	Leu	Thr	Leu	Pro	Leu	Gln	Ala	His	His	
				65					70					75	
Ala	Met	Glu	Lys	Met	Glu	Glu	Phe	Val	Tyr	Lys	Val	Trp	Glu	Gly	
				80					85					90	
Arg	Trp	Arg	Val	Ile	Pro	Tyr	Asp	Val	Leu	Pro	Asp	Trp	Leu	Lys	
				95					100					105	
Asp	Asn	Asp	Tyr	Leu	Leu	His	Gly	His	Arg	Pro	Pro	Met	Pro	Ser	
				110					115					120	
Phe	Arg	Ala	Cys	Phe	Lys	Ser	Ile	Phe	Arg	Ile	His	Thr	Glu	Thr	
				125					130					135	
Gly	Asn	Ile	Trp	Thr	His	Leu	Leu	Gly	Phe	Val	Leu	Phe	Leu	Phe	
				140					145					150	
Leu	Gly	Ile	Leu	Thr	Met	Leu	Arg	Pro	Asn	Met	Tyr	Phe	Met	Ala	
				155					160					165	
Pro	Leu	Gln	Glu	Lys	Val	Val	Phe	Gly	Met	Phe	Phe	Leu	Gly	Ala	
				170					175					180	
Val	Leu	Cys	Leu	Ser	Phe	Ser	Trp	Leu	Phe	His	Thr	Val	Tyr	Cys	
				185					190					195	
His	Ser	Glu	Lys	Val	Ser	Arg	Thr	Phe	Ser	Lys	Leu	Asp	Tyr	Ser	
				200					205					210	
Gly	Ile	Ala	Leu	Leu	Ile	Met	Gly	Ser	Phe	Val	Pro	Trp	Leu	Tyr	
				215					220					225	
Tyr	Ser	Phe	Tyr	Cys	Ser	Pro	Gln	Pro	Arg	Leu	Ile	Tyr	Leu	Ser	
				230					235					240	
Ile	Val	Cys	Val	Leu	Gly	Ile	Ser	Ala	Ile	Ile	Val	Ala	Gln	Trp	
				245					250					255	
Asp	Arg	Phe	Ala	Thr	Pro	Lys	His	Arg	Gln	Thr	Arg	Ala	Gly	Val	
				260					265					270	
Phe	Leu	Gly	Leu	Gly	Leu	Ser	Gly	Val	Val	Pro	Thr	Met	His	Phe	
				275					280					285	
Thr	Ile	Ala	Glu	Gly	Phe	Val	Lys	Ala	Thr	Thr	Val	Gly	Gln	Met	
				290					295					300	
Gly	Trp	Phe	Phe	Leu	Met	Ala	Val	Met	Tyr	Ile	Thr	Gly	Ala	Gly	
				305					310					315	
Leu	Tyr	Ala	Ala	Arg	Ile	Pro	Glu	Arg	Phe	Phe	Pro	Gly	Lys	Phe	
				320					325					330	
Asp	Ile	Trp	Phe	Gln	Ser	His	Gln	Ile	Phe	His	Val	Leu	Val	Val	
				335					340					345	
Ala	Ala	Ala	Phe	Val	His	Phe	Tyr	Gly	Val	Ser	Asn	Leu	Gln	Glu	
				350					355					360	
Phe	Arg	Tyr	Gly	Leu	Glu	Gly	Gly	Cys	Thr	Asp	Asp	Thr	Leu	Leu	
				365					370					375	

<210> 6

<211> 249

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2172512CD1

<400> 6

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Met Ser Gly Val Val Pro Thr Ala Pro Glu Gln Pro Ala Gly Glu
 1          5          10          15
Met Glu Asn Gln Thr Lys Pro Pro Asp Pro Arg Pro Asp Ala Pro
          20          25          30
Pro Glu Tyr Ser Ser His Phe Leu Pro Gly Pro Pro Gly Thr Ala
          35          40          45
Val Pro Pro Pro Thr Gly Tyr Pro Gly Gly Leu Pro Met Gly Tyr
          50          55          60
Tyr Ser Pro Gln Gln Pro Ser Thr Phe Pro Leu Tyr Gln Pro Val
          65          70          75
Gly Gly Ile His Pro Val Arg Tyr Gln Pro Gly Lys Tyr Pro Met
          80          85          90
Pro Asn Gln Ser Val Pro Ile Thr Trp Met Pro Gly Pro Thr Pro
          95          100          105
Met Ala Asn Cys Pro Pro Gly Leu Glu Tyr Leu Val Gln Leu Asp
          110          115          120
Asn Ile His Val Leu Gln His Phe Glu Pro Leu Glu Met Met Thr
          125          130          135
Cys Phe Glu Thr Asn Asn Arg Tyr Asp Ile Lys Asn Asn Ser Asp
          140          145          150
Gln Met Val Tyr Ile Val Thr Glu Asp Thr Asp Asp Phe Thr Arg
          155          160          165
Asn Ala Tyr Arg Thr Leu Arg Pro Phe Val Leu Arg Val Thr Asp
          170          175          180
Cys Met Gly Arg Glu Ile Met Thr Met Gln Arg Pro Phe Arg Cys
          185          190          195
Thr Cys Cys Cys Phe Cys Cys Pro Ser Ala Arg Gln Glu Leu Glu
          200          205          210
Val Gln Cys Pro Pro Gly Val Thr Ile Gly Phe Val Ala Glu His
          215          220          225
Trp Asn Leu Cys Arg Ala Val Tyr Ser Ile Gln Lys Lys Lys Lys
          230          235          240
Lys Ile Ala Ala Gln Ala Tyr Ser Leu
          245

```

<210> 7

<211> 353

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2483172CD1

<400> 7

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Met Ala Met Thr Leu Leu Glu Asp Trp Cys Arg Gly Met Asp Val
 1          5          10          15
Asn Ser Gln Arg Ala Leu Leu Val Trp Gly Ile Pro Val Asn Cys
          20          25          30
Asp Glu Ala Glu Ile Glu Glu Thr Leu Gln Ala Ala Met Pro Gln
          35          40          45
Val Ser Tyr Arg Met Leu Gly Arg Met Phe Trp Arg Glu Glu Asn
          50          55          60
Ala Lys Ala Ala Leu Leu Glu Leu Thr Gly Ala Val Asp Tyr Ala
          65          70          75
Ala Ile Pro Arg Glu Met Pro Gly Lys Gly Gly Val Trp Lys Val
          80          85          90
Leu Phe Lys Pro Pro Thr Ser Asp Ala Glu Phe Leu Glu Arg Leu
          95          100          105
His Leu Phe Leu Ala Arg Glu Gly Trp Thr Val Gln Asp Val Ala
          110          115          120
Arg Val Leu Gly Phe Gln Asn Pro Thr Pro Thr Pro Gly Pro Glu
          125          130          135

```

Met	Pro	Ala	Glu	Met	Leu	Asn	Tyr	Ile	Leu	Asp	Asn	Val	Ile	Gln	
				140					145					150	
Pro	Leu	Val	Glu	Ser	Ile	Trp	Tyr	Lys	Arg	Leu	Thr	Leu	Phe	Ser	
				155					160					165	
Gly	Arg	Asp	Ile	Pro	Gly	Pro	Gly	Glu	Glu	Thr	Phe	Asp	Pro	Trp	
				170					175					180	
Leu	Glu	His	Thr	Asn	Glu	Val	Leu	Glu	Glu	Trp	Gln	Val	Ser	Asp	
				185					190					195	
Val	Glu	Lys	Arg	Arg	Arg	Leu	Met	Glu	Ser	Leu	Arg	Gly	Pro	Ala	
				200					205					210	
Ala	Asp	Val	Ile	Arg	Ile	Leu	Lys	Ser	Asn	Asn	Pro	Ala	Ile	Thr	
				215					220					225	
Thr	Ala	Glu	Cys	Leu	Lys	Ala	Leu	Glu	Gln	Val	Phe	Gly	Ser	Val	
				230					235					240	
Glu	Ser	Ser	Arg	Asp	Ala	Gln	Ile	Lys	Phe	Leu	Asn	Thr	Tyr	Gln	
				245					250					255	
Asn	Pro	Gly	Glu	Lys	Leu	Ser	Ala	Tyr	Val	Ile	Arg	Leu	Glu	Pro	
				260					265					270	
Leu	Leu	Gln	Lys	Val	Val	Glu	Lys	Gly	Ala	Ile	Asp	Lys	Asp	Asn	
				275					280					285	
Val	Asn	Gln	Ala	Arg	Leu	Glu	Gln	Val	Ile	Ala	Gly	Ala	Asn	His	
				290					295					300	
Ser	Gly	Ala	Ile	Arg	Arg	Gln	Leu	Trp	Leu	Thr	Gly	Ala	Gly	Glu	
				305					310					315	
Gly	Pro	Ala	Pro	Asn	Leu	Phe	Gln	Leu	Leu	Val	Gln	Ile	Arg	Glu	
				320					325					330	
Glu	Glu	Ala	Lys	Glu	Glu	Glu	Glu	Glu	Ala	Glu	Ala	Thr	Leu	Leu	
				335					340					345	
Gln	Leu	Gly	Leu	Glu	Gly	His	Phe								
				350											

<210> 8

<211> 194

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2656128CD1

<400> 8

Met	His	Asp	Ser	Asn	Asn	Val	Glu	Lys	Asp	Ile	Thr	Pro	Ser	Glu	
1				5					10					15	
Leu	Pro	Ala	Asn	Pro	Gly	Cys	Leu	His	Ser	Lys	Glu	His	Ser	Ile	
				20					25					30	
Lys	Ala	Thr	Leu	Ile	Trp	Arg	Leu	Phe	Phe	Leu	Ile	Met	Phe	Leu	
				35					40					45	
Thr	Ile	Ile	Val	Cys	Gly	Met	Val	Ala	Ala	Leu	Ser	Ala	Ile	Arg	
				50					55					60	
Ala	Asn	Cys	His	Gln	Glu	Pro	Ser	Val	Cys	Leu	Gln	Ala	Ala	Cys	
				65					70					75	
Pro	Glu	Ser	Trp	Ile	Gly	Phe	Gln	Arg	Lys	Cys	Phe	Tyr	Phe	Ser	
				80					85					90	
Asp	Asp	Thr	Lys	Asn	Trp	Thr	Ser	Ser	Gln	Arg	Phe	Cys	Asp	Ser	
				95					100					105	
Gln	Asp	Ala	Asp	Leu	Ala	Gln	Val	Glu	Ser	Phe	Gln	Glu	Leu	Asn	
				110					115					120	
Phe	Leu	Leu	Arg	Tyr	Lys	Gly	Pro	Ser	Asp	His	Trp	Ile	Gly	Leu	
				125					130					135	
Ser	Arg	Glu	Gln	Gly	Gln	Pro	Trp	Lys	Trp	Ile	Asn	Gly	Thr	Glu	
				140					145					150	
Trp	Thr	Arg	Gln	Leu	Val	Met	Lys	Glu	Asp	Gly	Ala	Asn	Leu	Tyr	
				155					160					165	
Val	Ala	Lys	Val	Ser	Gln	Val	Pro	Arg	Met	Asn	Pro	Arg	Pro	Val	

	170		175		180
Met Val Ser Tyr	Pro Gly Ser Arg Arg	Val Cys Leu Phe Glu			
	185		190		

<210> 9

<211> 322

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 5855841CD1

<400> 9

Met Ser Ser Leu Gly Gly Gly Ser Gln Asp Ala Gly Gly Ser Ser		
1 5 10 15		
Ser Ser Ser Thr Asn Gly Ser Gly Gly Ser Gly Ser Ser Gly Pro		
20 25 30		
Lys Ala Gly Ala Ala Asp Lys Ser Ala Val Val Ala Ala Ala Ala		
35 40 45		
Pro Ala Ser Val Ala Asp Asp Thr Pro Pro Pro Glu Arg Arg Asn		
50 55 60		
Lys Ser Gly Ile Ile Ser Glu Pro Leu Asn Lys Ser Leu Arg Arg		
65 70 75		
Ser Arg Pro Leu Ser His Tyr Ser Ser Phe Gly Ser Ser Gly Gly		
80 85 90		
Ser Gly Gly Gly Ser Met Met Gly Gly Glu Ser Ala Asp Lys Ala		
95 100 105		
Thr Ala Ala Ala Ala Ala Ala Ser Leu Leu Ala Asn Gly His Asp		
110 115 120		
Leu Ala Ala Ala Met Ala Val Asp Lys Ser Asn Pro Thr Ser Lys		
125 130 135		
His Lys Ser Gly Ala Val Ala Ser Leu Leu Ser Lys Ala Glu Arg		
140 145 150		
Ala Thr Glu Leu Ala Ala Glu Gly Gln Leu Thr Leu Gln Gln Phe		
155 160 165		
Ala Gln Ser Thr Glu Met Leu Lys Arg Val Val Gln Glu His Leu		
170 175 180		
Pro Leu Met Ser Glu Ala Gly Ala Gly Leu Pro Asp Met Glu Ala		
185 190 195		
Val Ala Gly Ala Glu Ala Leu Asn Gly Gln Ser Asp Phe Pro Tyr		
200 205 210		
Leu Gly Ala Phe Pro Ile Asn Pro Gly Leu Phe Ile Met Thr Pro		
215 220 225		
Ala Gly Val Phe Leu Ala Glu Ser Ala Leu His Met Ala Gly Leu		
230 235 240		
Ala Glu Tyr Pro Met Gln Gly Glu Leu Ala Ser Ala Ile Ser Ser		
245 250 255		
Gly Lys Lys Lys Arg Lys Arg Cys Gly Met Cys Ala Pro Cys Arg		
260 265 270		
Arg Arg Ile Asn Cys Glu Gln Cys Ser Ser Cys Arg Asn Arg Lys		
275 280 285		
Thr Gly His Gln Ile Cys Lys Phe Arg Lys Cys Glu Glu Leu Lys		
290 295 300		
Lys Lys Pro Ser Ala Ala Leu Glu Lys Val Met Leu Pro Thr Gly		
305 310 315		
Ala Ala Phe Arg Trp Phe Gln		
320		

<210> 10

<211> 335

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 603462CD1

<400> 10

```

Met Leu Gln Gly His Ser Ser Val Phe Gln Ala Leu Leu Gly Thr
 1          5          10          15
Phe Phe Thr Trp Gly Met Thr Ala Ala Gly Ala Ala Leu Val Phe
 20          25          30
Val Phe Ser Ser Gly Gln Arg Arg Ile Leu Asp Gly Ser Leu Gly
 35          40          45
Phe Ala Ala Gly Val Met Leu Ala Ala Ser Tyr Trp Ser Leu Leu
 50          55          60
Ala Pro Ala Val Glu Met Ala Thr Ser Ser Gly Gly Phe Gly Ala
 65          70          75
Phe Ala Phe Phe Pro Val Ala Val Gly Phe Thr Leu Gly Ala Ala
 80          85          90
Phe Val Tyr Leu Ala Asp Leu Leu Met Pro His Leu Gly Ala Ala
 95          100         105
Glu Asp Pro Gln Thr Ala Leu Ala Leu Asn Phe Gly Ser Thr Leu
 110         115         120
Met Lys Lys Lys Ser Asp Pro Glu Gly Pro Ala Leu Leu Phe Pro
 125         130         135
Glu Ser Glu Leu Ser Ile Arg Ile Asp Lys Ser Glu Asn Gly Glu
 140         145         150
Ala Tyr Gln Arg Lys Lys Ala Ala Ala Thr Gly Leu Pro Glu Gly
 155         160         165
Pro Ala Val Pro Val Pro Ser Arg Gly Asn Leu Ala Gln Pro Gly
 170         175         180
Gly Ser Ser Trp Arg Arg Ile Ala Leu Leu Ile Leu Ala Ile Thr
 185         190         195
Ile His Asn Val Pro Glu Gly Leu Ala Val Gly Val Gly Phe Gly
 200         205         210
Ala Ile Glu Lys Thr Ala Ser Ala Thr Phe Glu Ser Ala Arg Asn
 215         220         225
Leu Ala Ile Gly Ile Gly Ile Gln Asn Phe Pro Glu Gly Leu Ala
 230         235         240
Val Ser Leu Pro Leu Arg Gly Ala Gly Phe Ser Thr Trp Arg Ala
 245         250         255
Phe Trp Tyr Gly Gln Leu Ser Gly Met Val Glu Pro Leu Ala Gly
 260         265         270
Val Phe Gly Ala Phe Ala Val Val Leu Ala Glu Pro Ile Leu Pro
 275         280         285
Tyr Ala Leu Ala Phe Ala Ala Gly Ala Met Val Tyr Val Val Met
 290         295         300
Asp Asp Ile Ile Pro Glu Ala Gln Ile Ser Gly Asn Gly Lys Leu
 305         310         315
Ala Ser Trp Ala Ser Ile Leu Gly Phe Val Val Met Met Ser Leu
 320         325         330
Asp Val Gly Leu Gly
 335

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<210> 11

<211> 620

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 747681CD1

<400> 11

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Met Gln Val Ser Lys Arg Met Leu Ala Gly Gly Val Arg Ser Met
 1          5          10          15
Pro Ser Pro Leu Leu Ala Cys Trp Gln Pro Ile Leu Leu Leu Val

```


	20		25		30
Leu Gly Ser Val	Leu Ser Gly Ser Ala Thr Gly Cys Pro Pro Arg				
	35		40		45
Cys Glu Cys Ser	Ala Gln Asp Arg Ala Val Leu Cys His Arg Lys				
	50		55		60
Arg Phe Val Ala	Val Pro Glu Gly Ile Pro Thr Glu Thr Arg Leu				
	65		70		75
Leu Asp Leu Gly	Lys Asn Arg Ile Lys Thr Leu Asn Gln Asp Glu				
	80		85		90
Phe Ala Ser Phe	Pro His Leu Glu Glu Leu Glu Leu Asn Glu Asn				
	95		100		105
Ile Val Ser Ala	Val Glu Pro Gly Ala Phe Asn Asn Leu Phe Asn				
	110		115		120
Leu Arg Thr Leu	Gly Leu Arg Ser Asn Arg Leu Lys Leu Ile Pro				
	125		130		135
Leu Gly Val Phe	Thr Gly Leu Ser Asn Leu Thr Lys Leu Asp Ile				
	140		145		150
Ser Glu Asn Lys	Ile Val Ile Leu Leu Asp Tyr Met Phe Gln Asp				
	155		160		165
Leu Tyr Asn Leu	Lys Ser Leu Glu Val Gly Asp Asn Asp Leu Val				
	170		175		180
Tyr Ile Ser His	Arg Ala Phe Ser Gly Leu Asn Ser Leu Glu Gln				
	185		190		195
Leu Thr Leu Glu	Lys Cys Asn Leu Thr Ser Ile Pro Thr Glu Ala				
	200		205		210
Leu Ser His Leu	His Gly Leu Ile Val Leu Arg Leu Arg His Leu				
	215		220		225
Asn Ile Asn Ala	Ile Arg Asp Tyr Ser Phe Lys Arg Leu Tyr Arg				
	230		235		240
Leu Lys Val Leu	Glu Ile Ser His Trp Pro Tyr Leu Asp Thr Met				
	245		250		255
Thr Pro Asn Cys	Leu Tyr Gly Leu Asn Leu Thr Ser Leu Ser Ile				
	260		265		270
Thr His Cys Asn	Leu Thr Ala Val Pro Tyr Leu Ala Val Arg His				
	275		280		285
Leu Val Tyr Leu	Arg Phe Leu Asn Leu Ser Tyr Asn Pro Ile Ser				
	290		295		300
Thr Ile Glu Gly	Ser Met Leu His Glu Leu Leu Arg Leu Gln Glu				
	305		310		315
Ile Gln Leu Val	Gly Gly Gln Leu Ala Val Val Glu Pro Tyr Ala				
	320		325		330
Phe Arg Gly Leu	Asn Tyr Leu Arg Val Leu Asn Val Ser Gly Asn				
	335		340		345
Gln Leu Thr Thr	Leu Glu Glu Ser Val Phe His Ser Val Gly Asn				
	350		355		360
Leu Glu Thr Leu	Ile Leu Asp Ser Asn Pro Leu Ala Cys Asp Cys				
	365		370		375
Arg Leu Leu Trp	Val Phe Arg Arg Arg Trp Arg Leu Asn Phe Asn				
	380		385		390
Arg Gln Gln Pro	Thr Cys Ala Thr Pro Glu Phe Val Gln Gly Lys				
	395		400		405
Glu Phe Lys Asp	Phe Pro Asp Val Leu Leu Pro Asn Tyr Phe Thr				
	410		415		420
Cys Arg Arg Ala	Arg Ile Arg Asp Arg Lys Ala Gln Gln Val Phe				
	425		430		435
Val Asp Glu Gly	His Thr Val Gln Phe Val Cys Arg Ala Asp Gly				
	440		445		450
Asp Pro Pro Pro	Ala Ile Leu Trp Leu Ser Pro Arg Lys His Leu				
	455		460		465
Val Ser Ala Lys	Ser Asn Gly Arg Leu Thr Val Phe Pro Asp Gly				
	470		475		480
Thr Leu Glu Val	Arg Tyr Ala Gln Val Gln Asp Asn Gly Thr Tyr				
	485		490		495

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Leu Cys Ile Ala Ala Asn Ala Gly Gly Asn Asp Ser Met Pro Ala
500 505 510
His Leu His Val Arg Ser Tyr Ser Pro Asp Trp Pro His Gln Pro
515 520 525
Asn Lys Thr Phe Ala Phe Ile Ser Asn Gln Pro Gly Glu Gly Glu
530 535 540
Ala Asn Ser Thr Arg Ala Thr Val Pro Phe Pro Phe Asp Ile Lys
545 550 555
Thr Leu Ile Ile Ala Thr Thr Met Gly Phe Ile Ser Phe Leu Gly
560 565 570
Val Val Leu Phe Cys Leu Val Leu Leu Phe Leu Trp Ser Arg Gly
575 580 585
Lys Gly Asn Thr Lys His Asn Ile Glu Ile Glu Tyr Val Pro Arg
590 595 600
Lys Ser Asp Ala Gly Ile Ser Ser Ala Asp Ala Pro Arg Lys Phe
605 610 615
Asn Met Lys Met Ile
620

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<210> 12

<211> 491

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 919469CD1

<400> 12

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Met Ala Gly Gln Gly Leu Pro Leu His Val Ala Thr Leu Leu Thr
1 5 10 15
Gly Leu Leu Glu Cys Leu Gly Phe Ala Gly Val Leu Phe Gly Trp
20 25 30
Pro Ser Leu Val Phe Val Phe Lys Asn Glu Asp Tyr Phe Lys Asp
35 40 45
Leu Cys Gly Pro Asp Ala Gly Pro Ile Gly Asn Ala Thr Gly Gln
50 55 60
Ala Asp Cys Lys Ala Gln Asp Glu Arg Phe Ser Leu Ile Phe Thr
65 70 75
Leu Gly Ser Phe Met Asn Asn Phe Met Thr Phe Pro Thr Gly Tyr
80 85 90
Ile Phe Asp Arg Phe Lys Thr Thr Val Ala Arg Leu Ile Ala Ile
95 100 105
Phe Phe Tyr Thr Thr Ala Thr Leu Ile Ile Ala Phe Thr Ser Ala
110 115 120
Gly Ser Ala Val Leu Leu Phe Leu Ala Met Pro Met Leu Thr Ile
125 130 135
Gly Gly Ile Leu Phe Leu Ile Thr Asn Leu Gln Ile Gly Asn Leu
140 145 150
Phe Gly Gln His Arg Ser Thr Ile Ile Thr Leu Tyr Asn Gly Ala
155 160 165
Phe Asp Ser Ser Ser Ala Val Phe Leu Ile Ile Lys Leu Leu Tyr
170 175 180
Glu Lys Gly Ile Ser Leu Arg Ala Ser Phe Ile Phe Ile Ser Val
185 190 195
Cys Ser Thr Trp His Val Ala Arg Thr Phe Leu Leu Met Pro Arg
200 205 210
Gly His Ile Pro Tyr Pro Leu Pro Pro Asn Tyr Ser Tyr Gly Leu
215 220 225
Cys Pro Gly Asn Gly Thr Thr Lys Glu Glu Lys Glu Thr Ala Glu
230 235 240
His Glu Asn Arg Glu Leu Gln Ser Lys Glu Phe Leu Ser Ala Lys
245 250 255
Glu Glu Thr Pro Gly Ala Gly Gln Lys Gln Glu Leu Arg Ser Phe

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260	265	270
Trp Ser Tyr Ala Phe Ser Arg Arg Phe	Ala Trp His Leu Val Trp	
275	280	285
Leu Ser Val Ile Gln Leu Trp His Tyr	Leu Phe Ile Gly Thr Leu	
290	295	300
Asn Ser Leu Leu Thr Asn Met Ala Gly	Gly Asp Met Ala Arg Val	
305	310	315
Ser Thr Tyr Thr Asn Ala Phe Ala Phe	Thr Gln Phe Gly Val Leu	
320	325	330
Cys Ala Pro Trp Asn Gly Leu Leu Met	Asp Arg Leu Lys Gln Lys	
335	340	345
Tyr Gln Lys Glu Ala Arg Lys Thr Gly	Ser Ser Thr Leu Ala Val	
350	355	360
Ala Leu Cys Ser Thr Val Pro Ser Leu	Ala Leu Thr Ser Leu Leu	
365	370	375
Cys Leu Gly Phe Ala Leu Cys Ala Ser	Val Pro Ile Leu Pro Leu	
380	385	390
Gln Tyr Leu Thr Phe Ile Leu Gln Val	Ile Ser Arg Ser Phe Leu	
395	400	405
Tyr Gly Ser Asn Ala Ala Phe Leu Thr	Leu Ala Phe Pro Ser Glu	
410	415	420
His Phe Gly Lys Leu Phe Gly Leu Val	Met Ala Leu Ser Ala Val	
425	430	435
Val Ser Leu Leu Gln Phe Pro Ile Phe	Thr Leu Ile Lys Gly Ser	
440	445	450
Leu Gln Asn Asp Pro Phe Tyr Val Asn	Val Met Phe Met Leu Ala	
455	460	465
Ile Leu Leu Thr Phe Phe His Pro Phe	Leu Val Tyr Arg Glu Cys	
470	475	480
Arg Thr Trp Lys Glu Ser Pro Ser Ala	Ile Ala	
485	490	

<210> 13

<211> 580

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 977658CD1

<400> 13

Met Thr Ala Pro Ala Gly Pro Arg Gly Ser Glu Thr Glu Arg Leu	
1 5 10 15	
Leu Thr Pro Asn Pro Gly Tyr Gly Thr Gln Ala Gly Pro Ser Pro	
20 25 30	
Ala Pro Pro Thr Pro Pro Glu Glu Glu Asp Leu Arg Arg Arg Leu	
35 40 45	
Lys Tyr Phe Phe Met Ser Pro Cys Asp Lys Phe Arg Ala Lys Gly	
50 55 60	
Arg Lys Pro Cys Lys Leu Met Leu Gln Val Val Lys Ile Leu Val	
65 70 75	
Val Thr Val Gln Leu Ile Leu Phe Gly Leu Ser Asn Gln Leu Ala	
80 85 90	
Val Thr Phe Arg Glu Glu Asn Thr Ile Ala Phe Arg His Leu Phe	
95 100 105	
Leu Leu Gly Tyr Ser Asp Gly Ala Asp Asp Thr Phe Ala Ala Tyr	
110 115 120	
Thr Arg Glu Gln Leu Tyr Gln Ala Ile Phe His Ala Val Asp Gln	
125 130 135	
Tyr Leu Ala Leu Pro Asp Val Ser Leu Gly Arg Tyr Ala Tyr Val	
140 145 150	
Arg Gly Gly Gly Asp Pro Trp Thr Asn Gly Ser Gly Leu Ala Leu	
155 160 165	

Cys	Gln	Arg	Tyr	Tyr	His	Arg	Gly	His	Val	Asp	Pro	Ala	Asn	Asp	
				170					175					180	
Thr	Phe	Asp	Ile	Asp	Pro	Met	Val	Val	Thr	Asp	Cys	Ile	Gln	Val	
				185					190					195	
Asp	Pro	Pro	Glu	Arg	Pro	Pro	Pro	Pro	Pro	Ser	Asp	Asp	Leu	Thr	
				200					205					210	
Leu	Leu	Glu	Ser	Ser	Ser	Ser	Tyr	Lys	Asn	Leu	Thr	Leu	Lys	Phe	
				215					220					225	
His	Lys	Leu	Val	Asn	Val	Thr	Ile	His	Phe	Arg	Leu	Lys	Thr	Ile	
				230					235					240	
Asn	Leu	Gln	Ser	Leu	Ile	Asn	Asn	Glu	Ile	Pro	Asp	Cys	Tyr	Thr	
				245					250					255	
Phe	Ser	Val	Leu	Ile	Thr	Phe	Asp	Asn	Lys	Ala	His	Ser	Gly	Arg	
				260					265					270	
Ile	Pro	Ile	Ser	Leu	Glu	Thr	Gln	Ala	His	Ile	Gln	Glu	Cys	Lys	
				275					280					285	
His	Pro	Ser	Val	Phe	Gln	His	Gly	Asp	Asn	Ser	Phe	Arg	Leu	Leu	
				290					295					300	
Phe	Asp	Val	Val	Val	Ile	Leu	Thr	Cys	Ser	Leu	Ser	Phe	Leu	Leu	
				305					310					315	
Cys	Ala	Arg	Ser	Leu	Leu	Arg	Gly	Phe	Leu	Leu	Gln	Asn	Glu	Phe	
				320					325					330	
Val	Gly	Phe	Met	Trp	Arg	Gln	Arg	Gly	Arg	Val	Ile	Ser	Leu	Trp	
				335					340					345	
Glu	Arg	Leu	Glu	Phe	Val	Asn	Gly	Trp	Tyr	Ile	Leu	Leu	Val	Thr	
				350					355					360	
Ser	Asp	Val	Leu	Thr	Ile	Ser	Gly	Thr	Ile	Met	Lys	Ile	Gly	Ile	
				365					370					375	
Glu	Ala	Lys	Asn	Leu	Ala	Ser	Tyr	Asp	Val	Cys	Ser	Ile	Leu	Leu	
				380					385					390	
Gly	Thr	Ser	Thr	Leu	Leu	Val	Trp	Val	Gly	Val	Ile	Arg	Tyr	Leu	
				395					400					405	
Thr	Phe	Phe	His	Asn	Tyr	Asn	Ile	Leu	Ile	Ala	Thr	Leu	Arg	Val	
				410					415					420	
Ala	Leu	Pro	Ser	Val	Met	Arg	Phe	Cys	Cys	Cys	Val	Ala	Val	Ile	
				425					430					435	
Tyr	Leu	Gly	Tyr	Cys	Phe	Cys	Gly	Trp	Ile	Val	Leu	Gly	Pro	Tyr	
				440					445					450	
His	Val	Lys	Phe	Arg	Ser	Leu	Ser	Met	Val	Ser	Glu	Cys	Leu	Phe	
				455					460					465	
Ser	Leu	Ile	Asn	Gly	Asp	Asp	Met	Phe	Val	Thr	Phe	Ala	Ala	Met	
				470					475					480	
Gln	Ala	Gln	Gln	Gly	Arg	Ser	Ser	Leu	Val	Trp	Leu	Phe	Ser	Gln	
				485					490					495	
Leu	Tyr	Leu	Tyr	Ser	Phe	Ile	Ser	Leu	Phe	Ile	Tyr	Met	Val	Leu	
				500					505					510	
Ser	Leu	Phe	Ile	Ala	Leu	Ile	Thr	Gly	Ala	Tyr	Asp	Thr	Ile	Lys	
				515					520					525	
His	Pro	Gly	Gly	Ala	Gly	Ala	Glu	Glu	Ser	Glu	Leu	Gln	Ala	Tyr	
				530					535					540	
Ile	Ala	Gln	Cys	Gln	Asp	Ser	Pro	Thr	Ser	Gly	Lys	Phe	Arg	Arg	
				545					550					555	
Gly	Ser	Gly	Ser	Ala	Cys	Ser	Leu	Leu	Cys	Cys	Cys	Gly	Arg	Asp	
				560					565					570	
Pro	Ser	Glu	Glu	His	Ser	Leu	Leu	Val	Asn						
				575					580						

<210> 14
 <211> 455
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature

<223> Incyte ID No: 1004703CD1

<400> 14

Met	Ser	Phe	Leu	Ile	Asp	Ser	Ser	Ile	Met	Ile	Thr	Ser	Gln	Ile
1				5					10					15
Leu	Phe	Phe	Gly	Phe	Gly	Trp	Leu	Phe	Phe	Met	Arg	Gln	Leu	Phe
			20						25					30
Lys	Asp	Tyr	Glu	Ile	Arg	Gln	Tyr	Val	Val	Gln	Val	Ile	Phe	Ser
			35						40					45
Val	Thr	Phe	Ala	Phe	Ser	Cys	Thr	Met	Phe	Glu	Leu	Ile	Ile	Phe
			50						55					60
Glu	Ile	Leu	Gly	Val	Leu	Asn	Ser	Ser	Ser	Arg	Tyr	Phe	His	Trp
			65						70					75
Lys	Met	Asn	Leu	Cys	Val	Ile	Leu	Leu	Ile	Leu	Val	Phe	Met	Val
			80						85					90
Pro	Phe	Tyr	Ile	Gly	Tyr	Phe	Ile	Val	Ser	Asn	Ile	Arg	Leu	Leu
			95						100					105
His	Lys	Gln	Arg	Leu	Leu	Phe	Ser	Cys	Leu	Leu	Trp	Leu	Thr	Phe
			110						115					120
Met	Tyr	Phe	Phe	Trp	Lys	Leu	Gly	Asp	Leu	Phe	Pro	Ile	Leu	Ser
			125						130					135
Pro	Lys	His	Gly	Ile	Leu	Ser	Ile	Glu	Gln	Leu	Ile	Ser	Arg	Val
			140						145					150
Gly	Val	Ile	Gly	Val	Thr	Leu	Met	Ala	Leu	Leu	Ser	Gly	Phe	Gly
			155						160					165
Ala	Val	Asn	Cys	Pro	Tyr	Thr	Tyr	Met	Ser	Tyr	Phe	Leu	Arg	Asn
			170						175					180
Val	Thr	Asp	Thr	Asp	Ile	Leu	Ala	Leu	Glu	Arg	Arg	Leu	Leu	Gln
			185						190					195
Thr	Met	Asp	Met	Ile	Ile	Ser	Lys	Lys	Lys	Arg	Met	Ala	Met	Ala
			200						205					210
Arg	Arg	Thr	Met	Phe	Gln	Lys	Gly	Glu	Val	His	Asn	Lys	Pro	Ser
			215						220					225
Gly	Phe	Trp	Gly	Met	Ile	Lys	Ser	Val	Thr	Thr	Ser	Ala	Ser	Gly
			230						235					240
Ser	Glu	Asn	Leu	Thr	Leu	Ile	Gln	Gln	Glu	Val	Asp	Ala	Leu	Glu
			245						250					255
Glu	Leu	Ser	Arg	Gln	Leu	Phe	Leu	Glu	Thr	Ala	Asp	Leu	Tyr	Ala
			260						265					270
Thr	Lys	Glu	Arg	Ile	Glu	Tyr	Ser	Lys	Thr	Phe	Lys	Gly	Lys	Tyr
			275						280					285
Phe	Asn	Phe	Leu	Gly	Tyr	Phe	Phe	Ser	Ile	Tyr	Cys	Val	Trp	Lys
			290						295					300
Ile	Phe	Met	Ala	Thr	Ile	Asn	Ile	Val	Phe	Asp	Arg	Val	Gly	Lys
			305						310					315
Thr	Asp	Pro	Val	Thr	Arg	Gly	Ile	Glu	Ile	Thr	Val	Asn	Tyr	Leu
			320						325					330
Gly	Ile	Gln	Phe	Asp	Val	Lys	Phe	Trp	Ser	Gln	His	Ile	Ser	Phe
			335						340					345
Ile	Leu	Val	Gly	Ile	Ile	Ile	Val	Thr	Ser	Ile	Arg	Gly	Leu	Leu
			350						355					360
Ile	Thr	Leu	Thr	Lys	Phe	Phe	Tyr	Ala	Ile	Ser	Ser	Ser	Lys	Ser
			365						370					375
Ser	Asn	Val	Ile	Val	Leu	Leu	Leu	Ala	Gln	Ile	Met	Gly	Met	Tyr
			380						385					390
Phe	Val	Ser	Ser	Val	Leu	Leu	Ile	Arg	Met	Ser	Met	Pro	Leu	Glu
			395						400					405
Tyr	Arg	Thr	Ile	Ile	Thr	Glu	Val	Leu	Gly	Glu	Leu	Gln	Phe	Asn
			410						415					420
Phe	Tyr	His	Arg	Trp	Phe	Asp	Val	Ile	Phe	Leu	Val	Ser	Ala	Leu
			425						430					435
Ser	Ser	Ile	Leu	Phe	Leu	Tyr	Leu	Ala	His	Lys	Gln	Ala	Pro	Glu
			440						445					450

Leu Val Val Thr Ala Thr Ala Ser Pro Pro Ala Gly Leu Leu Ser

	20		25		30
Leu Leu Thr Ser Gly Gln Gly Ala Leu Asp Gln Glu Ala Leu Gly					
	35		40		45
Gly Leu Leu Asn Thr Leu Ala Asp Arg Val His Cys Thr Asn Gly					
	50		55		60
Pro Cys Gly Lys Cys Leu Ser Val Glu Asp Ala Leu Gly Leu Gly					
	65		70		75
Glu Pro Glu Gly Ser Gly Leu Pro Pro Gly Pro Val Leu Glu Ala					
	80		85		90
Arg Tyr Val Ala Arg Leu Ser Ala Ala Ala Val Leu Tyr Leu Ser					
	95		100		105
Asn Pro Glu Gly Thr Cys Glu Asp Thr Arg Ala Gly Leu Trp Ala					
	110		115		120
Ser His Ala Asp His Leu Leu Ala Leu Leu Glu Ser Pro Lys Ala					
	125		130		135
Leu Thr Pro Gly Leu Ser Trp Leu Leu Gln Arg Met Gln Ala Arg					
	140		145		150
Ala Ala Gly Gln Thr Pro Lys Thr Ala Cys Val Asp Ile Pro Gln					
	155		160		165
Leu Leu Glu Glu Ala Val Gly Ala Gly Ala Pro Gly Ser Ala Gly					
	170		175		180
Gly Val Leu Ala Ala Leu Leu Asp His Val Arg Ser Gly Ser Cys					
	185		190		195
Phe His Ala Leu Pro Ser Pro Gln Tyr Phe Val Asp Phe Val Phe					
	200		205		210
Gln Gln His Ser Ser Glu Val Pro Met Thr Leu Ala Glu Leu Ser					
	215		220		225
Ala Leu Met Gln Arg Leu Gly Val Gly Arg Glu Ala His Ser Asp					
	230		235		240
His Ser His Arg His Arg Gly Ala Ser Ser Arg Asp Pro Val Pro					
	245		250		255
Leu Ile Ser Ser Ser Asn Ser Ser Ser Val Trp Asp Thr Val Cys					
	260		265		270
Leu Ser Ala Arg Asp Val Met Ala Ala Tyr Gly Leu Ser Glu Gln					
	275		280		285
Ala Gly Val Thr Pro Glu Ala Trp Ala Gln Leu Ser Pro Ala Leu					
	290		295		300
Leu Gln Gln Gln Leu Ser Gly Ala Cys Thr Ser Gln Ser Arg Pro					
	305		310		315
Pro Val Gln Asp Gln Leu Ser Gln Ser Glu Arg Tyr Leu Tyr Gly					
	320		325		330
Ser Leu Ala Thr Leu Leu Ile Cys Leu Cys Ala Val Phe Gly Leu					
	335		340		345
Leu Leu Leu Thr Cys Thr Gly Cys Arg Gly Val Thr His Tyr Ile					
	350		355		360
Leu Gln Thr Phe Leu Ser Leu Ala Val Gly Ala Leu Thr Gly Asp					
	365		370		375
Ala Val Leu His Leu Thr Pro Lys Val Leu Gly Leu His Thr His					
	380		385		390
Ser Glu Glu Gly Leu Ser Pro Gln Pro Thr Trp Arg Leu Leu Ala					
	395		400		405
Met Leu Ala Gly Leu Tyr Ala Phe Phe Leu Phe Glu Asn Leu Phe					
	410		415		420
Asn Leu Leu Leu Pro Arg Asp Pro Glu Asp Leu Glu Asp Gly Pro					
	425		430		435
Cys Gly His Ser Ser His Ser His Gly Gly His Ser His Gly Val					
	440		445		450
Ser Leu Gln Leu Ala Pro Ser Glu Leu Arg Gln Pro Lys Pro Pro					
	455		460		465
His Glu Gly Ser Arg Ala Asp Leu Val Ala Glu Glu Ser Pro Glu					
	470		475		480
Leu Leu Asn Pro Glu Pro Arg Arg Leu Ser Pro Glu Leu Arg Leu					
	485		490		495

Leu	Pro	Tyr	Met	Ile	Thr	Leu	Gly	Asp	Ala	Val	His	Asn	Phe	Ala	
				500					505					510	
Asp	Gly	Leu	Ala	Val	Gly	Ala	Ala	Phe	Ala	Ser	Ser	Trp	Lys	Thr	
				515					520					525	
Gly	Leu	Ala	Thr	Ser	Leu	Ala	Val	Phe	Cys	His	Glu	Leu	Pro	His	
				530					535					540	
Glu	Leu	Gly	Asp	Phe	Ala	Ala	Leu	Leu	His	Ala	Gly	Leu	Ser	Val	
				545					550					555	
Arg	Gln	Ala	Leu	Leu	Leu	Asn	Leu	Ala	Ser	Ala	Leu	Thr	Ala	Phe	
				560					565					570	
Ala	Gly	Leu	Tyr	Val	Ala	Leu	Ala	Val	Gly	Val	Ser	Glu	Glu	Ser	
				575					580					585	
Glu	Ala	Trp	Ile	Leu	Ala	Val	Ala	Thr	Gly	Leu	Phe	Leu	Tyr	Val	
				590					595					600	
Ala	Leu	Cys	Asp	Met	Leu	Pro	Ala	Met	Leu	Lys	Val	Arg	Asp	Pro	
				605					610					615	
Arg	Pro	Trp	Leu	Leu	Phe	Leu	Leu	His	Asn	Val	Gly	Leu	Leu	Gly	
				620					625					630	
Gly	Trp	Thr	Val	Leu	Leu	Leu	Leu	Ser	Leu	Tyr	Glu	Asp	Asp	Ile	
				635					640					645	

Thr Phe

<210> 17

<211> 406

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1452856CD1

<400> 17

Met	Ala	Glu	Asn	Gly	Lys	Asn	Cys	Asp	Gln	Arg	Arg	Val	Ala	Met	
1				5					10					15	
Asn	Lys	Glu	His	His	Asn	Gly	Asn	Phe	Thr	Asp	Pro	Ser	Ser	Val	
				20					25					30	
Asn	Glu	Lys	Lys	Arg	Arg	Glu	Arg	Glu	Glu	Arg	Gln	Asn	Ile	Val	
				35					40					45	
Leu	Trp	Arg	Gln	Pro	Leu	Ile	Thr	Leu	Gln	Tyr	Phe	Ser	Leu	Glu	
				50					55					60	
Ile	Leu	Val	Ile	Leu	Lys	Glu	Trp	Thr	Ser	Lys	Leu	Trp	His	Arg	
				65					70					75	
Gln	Ser	Ile	Val	Val	Ser	Phe	Leu	Leu	Leu	Leu	Ala	Val	Leu	Ile	
				80					85					90	
Ala	Thr	Tyr	Tyr	Val	Glu	Gly	Val	His	Gln	Gln	Tyr	Val	Gln	Arg	
				95					100					105	
Ile	Glu	Lys	Gln	Phe	Leu	Leu	Tyr	Ala	Tyr	Trp	Ile	Gly	Leu	Gly	
				110					115					120	
Ile	Leu	Ser	Ser	Val	Gly	Leu	Gly	Thr	Gly	Leu	His	Thr	Phe	Leu	
				125					130					135	
Leu	Tyr	Leu	Gly	Pro	His	Ile	Ala	Ser	Val	Thr	Leu	Ala	Ala	Tyr	
				140					145					150	
Glu	Cys	Asn	Ser	Val	Asn	Phe	Pro	Glu	Pro	Pro	Tyr	Pro	Asp	Gln	
				155					160					165	
Ile	Ile	Cys	Pro	Asp	Glu	Glu	Gly	Thr	Glu	Gly	Thr	Ile	Ser	Leu	
				170					175					180	
Trp	Ser	Ile	Ile	Ser	Lys	Val	Arg	Ile	Glu	Ala	Cys	Met	Trp	Gly	
				185					190					195	
Ile	Gly	Thr	Ala	Ile	Gly	Glu	Leu	Pro	Pro	Tyr	Phe	Met	Ala	Arg	
				200					205					210	
Ala	Ala	Arg	Leu	Ser	Gly	Ala	Glu	Pro	Asp	Asp	Glu	Glu	Tyr	Gln	
				215					220					225	
Glu	Phe	Glu	Glu	Met	Leu	Glu	His	Ala	Glu	Ser	Ala	Gln	Asp	Phe	

230	235	240
Ala Ser Arg Ala Lys Leu Ala Val Gln Lys Leu Val Gln Lys Val		
245	250	255
Gly Phe Phe Gly Ile Leu Ala Cys Ala Ser Ile Pro Asn Pro Leu		
260	265	270
Phe Asp Leu Ala Gly Ile Thr Cys Gly His Phe Leu Val Pro Phe		
275	280	285
Trp Thr Phe Phe Gly Ala Thr Leu Ile Gly Lys Ala Ile Ile Lys		
290	295	300
Met His Ile Gln Lys Ile Phe Val Ile Ile Thr Phe Ser Lys His		
305	310	315
Ile Val Glu Gln Met Val Ala Phe Ile Gly Ala Val Pro Gly Ile		
320	325	330
Gly Pro Ser Leu Gln Lys Pro Phe Gln Glu Tyr Leu Glu Ala Gln		
335	340	345
Arg Gln Lys Leu His His Lys Ser Glu Met Gly Thr Pro Gln Gly		
350	355	360
Glu Asn Trp Leu Ser Trp Met Phe Glu Lys Leu Val Val Val Met		
365	370	375
Val Cys Tyr Phe Ile Leu Ser Ile Ile Asn Ser Met Ala Gln Ser		
380	385	390
Tyr Ala Lys Arg Ile Gln Gln Arg Leu Asn Ser Glu Glu Lys Thr		
395	400	405
Lys		

<210> 18
 <211> 290
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1562471CD1

<400> 18

Met Pro Leu Leu Thr Leu Tyr Leu Leu Leu Phe Trp Leu Ser Gly	
1 5 10 15	
Tyr Ser Ile Ala Thr Gln Ile Thr Gly Pro Thr Thr Val Asn Gly	
20 25 30	
Leu Glu Arg Gly Ser Leu Thr Val Gln Cys Val Tyr Arg Ser Gly	
35 40 45	
Trp Glu Thr Tyr Leu Lys Trp Trp Cys Arg Gly Ala Ile Trp Arg	
50 55 60	
Asp Cys Lys Ile Leu Val Lys Thr Ser Gly Ser Glu Gln Glu Val	
65 70 75	
Lys Arg Asp Arg Val Ser Ile Lys Asp Asn Gln Lys Asn Arg Thr	
80 85 90	
Phe Thr Val Thr Met Glu Asp Leu Met Lys Thr Asp Ala Asp Thr	
95 100 105	
Tyr Trp Cys Gly Ile Glu Lys Thr Gly Asn Asp Leu Gly Val Thr	
110 115 120	
Val Gln Val Thr Ile Asp Pro Ala Pro Val Thr Gln Glu Glu Thr	
125 130 135	
Ser Ser Ser Pro Thr Leu Thr Gly His His Leu Asp Asn Arg His	
140 145 150	
Lys Leu Leu Lys Leu Ser Val Leu Leu Pro Leu Ile Phe Thr Ile	
155 160 165	
Leu Leu Leu Leu Leu Val Ala Ala Ser Leu Leu Ala Trp Arg Met	
170 175 180	
Met Lys Tyr Gln Gln Lys Ala Ala Gly Met Ser Pro Glu Gln Val	
185 190 195	
Leu Gln Pro Leu Glu Gly Asp Leu Cys Tyr Ala Asp Leu Thr Leu	
200 205 210	

Gln	Leu	Ala	Gly	Thr	Ser	Pro	Arg	Lys	Ala	Thr	Thr	Lys	Leu	Ser
				215					220					225
Ser	Ala	Gln	Val	Asp	Gln	Val	Glu	Val	Glu	Tyr	Val	Thr	Met	Ala
				230					235					240
Ser	Leu	Pro	Lys	Glu	Asp	Ile	Ser	Tyr	Ala	Ser	Leu	Thr	Leu	Gly
				245					250					255
Ala	Glu	Asp	Gln	Glu	Pro	Thr	Tyr	Cys	Asn	Met	Gly	His	Leu	Ser
				260					265					270
Ser	His	Leu	Pro	Gly	Arg	Gly	Pro	Glu	Glu	Pro	Thr	Glu	Tyr	Ser
				275					280					285
Thr	Ile	Ser	Arg	Pro										
				290										

<210> 19

<211> 390

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1618158CD1

<400> 19

Met	Phe	Ser	Thr	Asn	Tyr	Ser	His	Met	Glu	Asn	Tyr	Arg	Lys	Arg
1				5					10					15
Glu	Asp	Leu	Val	Tyr	Gln	Ser	Thr	Val	Arg	Leu	Pro	Glu	Val	Arg
				20					25					30
Ile	Ser	Asp	Asn	Gly	Pro	Tyr	Glu	Cys	His	Val	Gly	Ile	Tyr	Asp
				35					40					45
Arg	Ala	Thr	Arg	Glu	Lys	Val	Val	Leu	Ala	Ser	Gly	Asn	Ile	Phe
				50					55					60
Leu	Asn	Val	Met	Ala	Pro	Pro	Thr	Ser	Ile	Glu	Val	Val	Ala	Ala
				65					70					75
Asp	Thr	Pro	Ala	Pro	Phe	Ser	Arg	Tyr	Gln	Ala	Gln	Asn	Phe	Thr
				80					85					90
Leu	Val	Cys	Ile	Val	Ser	Gly	Gly	Lys	Pro	Ala	Pro	Met	Val	Tyr
				95					100					105
Phe	Lys	Arg	Asp	Gly	Glu	Pro	Ile	Asp	Ala	Val	Pro	Leu	Ser	Glu
				110					115					120
Pro	Pro	Ala	Ala	Ser	Ser	Gly	Pro	Leu	Gln	Asp	Ser	Arg	Pro	Phe
				125					130					135
Arg	Ser	Leu	Leu	His	Arg	Asp	Leu	Asp	Asp	Thr	Lys	Met	Gln	Lys
				140					145					150
Ser	Leu	Ser	Leu	Leu	Asp	Ala	Glu	Asn	Arg	Gly	Gly	Arg	Pro	Tyr
				155					160					165
Thr	Glu	Arg	Pro	Ser	Arg	Gly	Leu	Thr	Pro	Asp	Pro	Asn	Ile	Leu
				170					175					180
Leu	Gln	Pro	Thr	Thr	Glu	Asn	Ile	Pro	Glu	Thr	Val	Val	Ser	Arg
				185					190					195
Glu	Phe	Pro	Arg	Trp	Val	His	Ser	Ala	Glu	Pro	Thr	Tyr	Phe	Leu
				200					205					210
Arg	His	Ser	Arg	Thr	Pro	Ser	Ser	Asp	Gly	Thr	Val	Glu	Val	Arg
				215					220					225
Ala	Leu	Leu	Thr	Trp	Thr	Leu	Asn	Pro	Gln	Ile	Asp	Asn	Glu	Ala
				230					235					240
Leu	Phe	Ser	Cys	Glu	Val	Lys	His	Pro	Ala	Leu	Ser	Met	Pro	Met
				245					250					255
Gln	Ala	Glu	Val	Thr	Leu	Val	Ala	Pro	Lys	Gly	Pro	Lys	Ile	Val
				260					265					270
Met	Thr	Pro	Ser	Arg	Ala	Arg	Val	Gly	Asp	Thr	Val	Arg	Ile	Leu
				275					280					285
Val	His	Gly	Phe	Gln	Asn	Glu	Val	Phe	Pro	Glu	Pro	Met	Phe	Thr
				290					295					300
Trp	Thr	Arg	Val	Gly	Ser	Arg	Leu	Leu	Asp	Gly	Ser	Ala	Glu	Phe

305	310	315
Asp Gly Lys Glu Leu Val Leu Glu Arg Val Pro Ala Glu Leu Asn		
320	325	330
Gly Ser Met Tyr Arg Cys Thr Ala Gln Asn Pro Leu Gly Ser Thr		
335	340	345
Asp Thr His Thr Arg Leu Ile Val Phe Glu Asn Pro Asn Ile Pro		
350	355	360
Arg Gly Thr Glu Asp Ser Asn Gly Ser Ile Gly Pro Thr Gly Ala		
365	370	375
Arg Leu Thr Leu Val Leu Ala Leu Thr Val Ile Leu Glu Leu Thr		
380	385	390

<210> 20

<211> 427

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1656935CD1

<400> 20

Met Asn Val Asn Ser Met Asp Met Thr Gly Gly Leu Ser Val Lys		
1	5	10
Asp Pro Ser Gln Ser Gln Ser Arg Leu Pro Gln Trp Thr His Pro		
20	25	30
Asn Ser Met Asp Asn Leu Pro Ser Ala Ala Ser Pro Leu Glu Gln		
35	40	45
Asn Pro Ser Lys His Gly Ala Ile Pro Gly Gly Leu Ser Ile Gly		
50	55	60
Pro Pro Gly Lys Ser Ser Ile Asp Asp Ser Tyr Gly Arg Tyr Asp		
65	70	75
Leu Ile Gln Asn Ser Glu Ser Pro Ala Ser Pro Pro Val Ala Val		
80	85	90
Pro His Ser Trp Ser Arg Ala Lys Ser Asp Ser Asp Lys Ile Ser		
95	100	105
Asn Gly Ser Ser Ile Asn Trp Pro Pro Glu Phe His Pro Gly Val		
110	115	120
Pro Trp Lys Gly Leu Gln Asn Ile Asp Pro Glu Asn Asp Pro Asp		
125	130	135
Val Thr Pro Gly Ser Val Pro Thr Gly Pro Thr Ile Asn Thr Thr		
140	145	150
Ile Gln Asp Val Asn Arg Tyr Leu Leu Lys Ser Gly Gly Ser Ser		
155	160	165
Pro Pro Ser Ser Gln Asn Ala Thr Leu Pro Ser Ser Ser Ala Trp		
170	175	180
Pro Leu Ser Ala Ser Gly Tyr Ser Ser Ser Phe Ser Ser Ile Ala		
185	190	195
Ser Ala Pro Ser Val Ala Gly Lys Leu Ser Asp Ile Lys Ser Thr		
200	205	210
Trp Ser Ser Gly Pro Thr Ser His Thr Gln Ala Ser Leu Ser His		
215	220	225
Glu Leu Trp Lys Val Pro Arg Asn Ser Thr Ala Pro Thr Arg Pro		
230	235	240
Pro Pro Gly Leu Thr Asn Pro Lys Pro Ser Ser Thr Trp Gly Ala		
245	250	255
Ser Pro Leu Gly Trp Thr Ser Ser Tyr Ser Ser Gly Ser Ala Trp		
260	265	270
Ser Thr Asp Thr Ser Gly Arg Thr Ser Ser Trp Leu Val Leu Arg		
275	280	285
Asn Leu Thr Pro Gln Ile Asp Gly Ser Lys Leu Arg Thr Leu Cys		
290	295	300
Leu Gln His Gly Pro Leu Ile Thr Phe His Leu Asn Leu Thr Gln		

	305		310		315
Gly Asn Ala Val	Val Arg Tyr Ser Ser	Lys Glu Glu Gly Leu Pro			
	320		325		330
Lys Ala Gln Glu	Val Leu Cys Thr Ile	Val Arg Pro Trp Glu Thr			
	335		340		345
Leu Ser His Ser	Leu Gly Pro Ser Phe	Arg Leu Val Gly Thr Lys			
	350		355		360
Glu Val Gly Ile	Arg Val Ser Phe Lys	Pro Pro Glu Gly Pro Gly			
	365		370		375
Arg Ile Gly Gln	Ser Thr Ile Phe Gln	Gly Leu Ala Gln Phe His			
	380		385		390
Asp Gln Arg Gly	Val Ser Lys Leu Thr	Gly Arg Gly Gly Ile His			
	395		400		405
Arg Pro Arg Gly	Arg Gly Lys Ala Ser	His Gln Leu Ala His Met			
	410		415		420
Arg His Cys Glu	Leu Thr Phe				
	425				

<210> 21

<211> 459

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1859305CD1

<400> 21

Met Glu Lys Thr Cys	Ile Asp Ala Leu Pro	Leu Thr Met Asn Ser
1	5	10
Ser Glu Lys Gln Glu	Thr Val Cys Ile Phe	Gly Thr Gly Asp Phe
	20	25
Gly Arg Ser Leu Gly	Leu Lys Met Leu Gln	Cys Gly Tyr Ser Val
	35	40
Val Phe Gly Ser Arg	Asn Pro Gln Lys Thr	Thr Leu Leu Pro Ser
	50	55
Gly Ala Glu Val Leu	Ser Tyr Ser Glu Ala	Ala Lys Lys Ser Asp
	65	70
Ile Ile Ile Ile Ala	Ile His Arg Glu His	Tyr Asp Phe Leu Thr
	80	85
Glu Leu Thr Glu Val	Leu Asn Gly Lys Ile	Leu Val Asp Ile Ser
	95	100
Asn Asn Leu Lys Ile	Asn Gln Tyr Pro Glu	Ser Asn Ala Glu Tyr
	110	115
Leu Ala His Leu Val	Pro Gly Ala His Val	Val Lys Ala Phe Asn
	125	130
Thr Ile Ser Ala Trp	Ala Leu Gln Ser Gly	Ala Leu Asp Ala Ser
	140	145
Arg Gln Val Phe Val	Cys Gly Asn Asp Ser	Lys Ala Lys Gln Arg
	155	160
Val Met Asp Ile Val	Arg Asn Leu Gly Leu	Thr Pro Met Asp Gln
	170	175
Gly Ser Leu Met Ala	Lys Glu Ile Glu Lys	Tyr Pro Leu Gln
	185	190
Leu Phe Pro Met Trp	Arg Phe Pro Phe Tyr	Leu Ser Ala Val Leu
	200	205
Cys Val Phe Leu Phe	Phe Tyr Cys Val Ile	Arg Asp Val Ile Tyr
	215	220
Pro Tyr Val Tyr Glu	Lys Lys Asp Asn Thr	Phe Arg Met Ala Ile
	230	235
Ser Ile Pro Asn Arg	Ile Phe Pro Ile Thr	Ala Leu Thr Leu Leu
	245	250
Ala Leu Val Tyr Leu	Pro Gly Val Ile Ala	Ala Ile Leu Gln Leu
	260	265

Tyr	Arg	Gly	Thr	Lys	Tyr	Arg	Arg	Phe	Pro	Asp	Trp	Leu	Asp	His	
				275					280					285	
Trp	Met	Leu	Cys	Arg	Lys	Gln	Leu	Gly	Leu	Val	Ala	Leu	Gly	Phe	
				290					295					300	
Ala	Phe	Leu	His	Val	Leu	Tyr	Thr	Leu	Val	Ile	Pro	Ile	Arg	Tyr	
				305					310					315	
Tyr	Val	Arg	Trp	Arg	Leu	Gly	Asn	Leu	Thr	Val	Thr	Gln	Ala	Ile	
				320					325					330	
Leu	Lys	Lys	Glu	Asn	Pro	Phe	Ser	Thr	Ser	Ser	Ala	Trp	Leu	Ser	
				335					340					345	
Asp	Ser	Tyr	Val	Ala	Leu	Gly	Ile	Leu	Gly	Phe	Phe	Leu	Phe	Val	
				350					355					360	
Leu	Leu	Gly	Ile	Thr	Ser	Leu	Pro	Ser	Val	Ser	Asn	Ala	Val	Asn	
				365					370					375	
Trp	Arg	Glu	Phe	Arg	Phe	Val	Gln	Ser	Lys	Leu	Gly	Tyr	Leu	Thr	
				380					385					390	
Leu	Ile	Leu	Cys	Thr	Ala	His	Thr	Leu	Val	Tyr	Gly	Gly	Lys	Arg	
				395					400					405	
Phe	Leu	Ser	Pro	Ser	Asn	Leu	Arg	Trp	Tyr	Leu	Pro	Ala	Ala	Tyr	
				410					415					420	
Val	Leu	Gly	Leu	Ile	Ile	Pro	Cys	Thr	Val	Leu	Val	Ile	Lys	Phe	
				425					430					435	
Val	Leu	Ile	Met	Pro	Cys	Val	Asp	Asn	Thr	Leu	Thr	Arg	Ile	Arg	
				440					445					450	
Gln	Gly	Trp	Glu	Arg	Asn	Ser	Lys	His							
				455											

<210> 22

<211> 229

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1949083CD1

<400> 22

Met	Leu	Pro	Val	Ser	Arg	Thr	Cys	Leu	Leu	Glu	Ser	Ser	Thr	Arg	
1				5					10					15	
Leu	Lys	Pro	His	Glu	Ala	Gln	Asn	Tyr	Arg	Lys	Lys	Ala	Leu	Trp	
				20					25					30	
Val	Ser	Trp	Phe	Ser	Ile	Ile	Val	Thr	Leu	Ala	Leu	Ala	Val	Ala	
				35					40					45	
Ala	Phe	Thr	Val	Ser	Val	Met	Arg	Tyr	Ser	Ala	Ser	Ala	Phe	Gly	
				50					55					60	
Phe	Ala	Phe	Asp	Ala	Ile	Leu	Asp	Val	Leu	Ser	Ser	Ala	Ile	Val	
				65					70					75	
Leu	Trp	Arg	Tyr	Ser	Asn	Ala	Ala	Ala	Val	His	Ser	Ala	His	Arg	
				80					85					90	
Glu	Tyr	Ile	Ala	Cys	Val	Ile	Leu	Gly	Val	Ile	Phe	Leu	Leu	Ser	
				95					100					105	
Ser	Ile	Cys	Ile	Val	Val	Lys	Ala	Ile	His	Asp	Leu	Ser	Thr	Arg	
				110					115					120	
Leu	Leu	Pro	Glu	Val	Asp	Asp	Phe	Leu	Phe	Ser	Val	Ser	Ile	Leu	
				125					130					135	
Ser	Gly	Ile	Leu	Cys	Ser	Ile	Leu	Ala	Val	Leu	Lys	Phe	Met	Leu	
				140					145					150	
Gly	Lys	Val	Leu	Thr	Ser	Arg	Ala	Leu	Ile	Thr	Asp	Gly	Phe	Asn	
				155					160					165	
Ser	Leu	Val	Gly	Gly	Val	Met	Gly	Phe	Ser	Ile	Leu	Leu	Ser	Ala	
				170					175					180	
Glu	Val	Phe	Lys	His	Asp	Ser	Ala	Val	Trp	Tyr	Leu	Asp	Gly	Ser	
				185					190					195	
Ile	Gly	Val	Leu	Ile	Gly	Leu	Thr	Ile	Phe	Ala	Tyr	Gly	Val	Lys	

	200		205		210
Leu Leu Ile Asp Met Val Pro Lys Val Arg Gln Thr Arg His Tyr					
	215		220		225
Glu Met Phe Glu					

<210> 23
 <211> 311
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 1996357CD1

<400> 23
 Met Ala Val Asp Ile Gln Pro Ala Cys Leu Gly Leu Tyr Cys Gly
 1 5 10 15
 Lys Thr Leu Leu Phe Lys Asn Gly Ser Thr Glu Ile Tyr Gly Glu
 20 25 30
 Cys Gly Val Cys Pro Arg Gly Gln Arg Thr Asn Ala Gln Lys Tyr
 35 40 45
 Cys Gln Pro Cys Thr Glu Ser Pro Glu Leu Tyr Asp Trp Leu Tyr
 50 55 60
 Leu Gly Phe Met Ala Met Leu Pro Leu Val Leu His Trp Phe Phe
 65 70 75
 Ile Glu Trp Tyr Ser Gly Lys Lys Ser Ser Ser Ala Leu Phe Gln
 80 85 90
 His Ile Thr Ala Leu Phe Glu Cys Ser Met Ala Ala Ile Ile Thr
 95 100 105
 Leu Leu Val Ser Asp Pro Val Gly Val Leu Tyr Ile Arg Ser Cys
 110 115 120
 Arg Val Leu Met Leu Ser Asp Trp Tyr Thr Met Leu Tyr Asn Pro
 125 130 135
 Ser Pro Asp Tyr Val Thr Thr Val His Cys Thr His Glu Ala Val
 140 145 150
 Tyr Pro Leu Tyr Thr Ile Val Phe Ile Tyr Tyr Ala Phe Cys Leu
 155 160 165
 Val Leu Met Met Leu Leu Arg Pro Leu Leu Val Lys Lys Ile Ala
 170 175 180
 Cys Gly Leu Gly Lys Ser Asp Arg Phe Lys Ser Ile Tyr Ala Ala
 185 190 195
 Leu Tyr Phe Phe Pro Ile Leu Thr Val Leu Gln Ala Val Gly Gly
 200 205 210
 Gly Leu Leu Tyr Tyr Ala Phe Pro Tyr Ile Ile Leu Val Leu Ser
 215 220 225
 Leu Val Thr Leu Ala Val Tyr Met Ser Ala Ser Glu Ile Glu Asn
 230 235 240
 Cys Tyr Asp Leu Leu Val Arg Lys Lys Arg Leu Ile Val Leu Phe
 245 250 255
 Ser His Trp Leu Leu His Ala Tyr Gly Ile Ile Ser Ile Ser Arg
 260 265 270
 Val Asp Lys Leu Glu Gln Asp Leu Pro Leu Leu Ala Leu Val Pro
 275 280 285
 Thr Pro Ala Leu Phe Tyr Leu Phe Thr Ala Lys Phe Thr Glu Pro
 290 295 300
 Ser Arg Ile Leu Ser Glu Gly Ala Asn Gly His
 305 310

<210> 24
 <211> 92
 <212> PRT
 <213> Homo sapiens

<220>

<221> misc_feature
 <223> Incyte ID No: 2061330CD1

<400> 24

Met	Arg	Phe	Ile	Phe	Leu	Lys	Phe	Trp	Thr	Tyr	Thr	Val	Arg	Ala	
1				5					10					15	
Ser	Thr	Asp	Leu	Thr	Gln	Thr	Gly	Asp	Cys	Ser	Gln	Cys	Thr	His	
				20					25					30	
Gln	Val	Thr	Glu	Val	Gly	Gln	Gln	Ile	Lys	Thr	Ile	Phe	Leu	Phe	
				35					40					45	
Tyr	Ser	Tyr	Tyr	Glu	Cys	Met	Glu	Thr	Ile	Lys	Glu	Thr	Cys	Leu	
				50					55					60	
Tyr	Asn	Ala	Thr	Gln	Tyr	Lys	Val	Cys	Ser	Pro	Arg	Asn	Asp	Arg	
				65					70					75	
Pro	Asp	Val	Cys	Tyr	Asn	Pro	Ser	Glu	Pro	Pro	Ala	Pro	Pro	Phe	
				80					85					90	

Leu Lys

<210> 25

<211> 258

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2346947CD1

<400> 25

Met	Ala	Glu	Ser	Pro	Gly	Cys	Cys	Ser	Val	Trp	Ala	Arg	Cys	Leu	
1				5					10					15	
His	Cys	Leu	Tyr	Ser	Cys	His	Trp	Arg	Lys	Cys	Pro	Arg	Glu	Arg	
				20					25					30	
Met	Gln	Thr	Ser	Lys	Cys	Asp	Cys	Ile	Trp	Phe	Gly	Leu	Leu	Phe	
				35					40					45	
Leu	Thr	Phe	Leu	Leu	Ser	Leu	Ser	Trp	Leu	Tyr	Ile	Gly	Leu	Val	
				50					55					60	
Leu	Leu	Asn	Asp	Leu	His	Asn	Phe	Asn	Glu	Phe	Leu	Phe	Arg	Arg	
				65					70					75	
Trp	Gly	His	Trp	Met	Asp	Trp	Ser	Leu	Ala	Phe	Leu	Leu	Val	Ile	
				80					85					90	
Ser	Leu	Leu	Val	Thr	Tyr	Ala	Ser	Leu	Leu	Leu	Val	Leu	Ala	Leu	
				95					100					105	
Leu	Leu	Arg	Leu	Cys	Arg	Gln	Pro	Leu	His	Leu	His	Ser	Leu	His	
				110					115					120	
Lys	Val	Leu	Leu	Leu	Leu	Ile	Met	Leu	Leu	Val	Ala	Ala	Gly	Leu	
				125					130					135	
Val	Gly	Leu	Asp	Ile	Gln	Trp	Gln	Gln	Glu	Trp	His	Ser	Leu	Arg	
				140					145					150	
Val	Ser	Leu	Gln	Ala	Thr	Ala	Pro	Phe	Leu	His	Ile	Gly	Ala	Ala	
				155					160					165	
Ala	Gly	Ile	Ala	Leu	Leu	Ala	Trp	Pro	Val	Ala	Asp	Thr	Phe	Tyr	
				170					175					180	
Arg	Ile	His	Arg	Arg	Gly	Pro	Lys	Ile	Leu	Leu	Leu	Leu	Leu	Phe	
				185					190					195	
Phe	Gly	Val	Val	Leu	Val	Ile	Tyr	Leu	Ala	Pro	Leu	Cys	Ile	Ser	
				200					205					210	
Ser	Pro	Cys	Ile	Met	Glu	Pro	Arg	Asp	Leu	Pro	Pro	Lys	Pro	Gly	
				215					220					225	
Leu	Val	Gly	His	Arg	Gly	Ala	Pro	Met	Leu	Ala	Pro	Glu	Asn	Thr	
				230					235					240	
Leu	Met	Ser	Leu	Arg	Lys	Thr	Ala	Glu	Cys	Gly	Leu	Leu	Cys	Leu	
				245					250					255	

Arg Leu Met

<210> 26
 <211> 226
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2795577CD1

<400> 26
 Met Lys Met Val Ala Pro Trp Thr Arg Phe Tyr Ser Asn Ser Cys
 1 5 10 15
 Cys Leu Cys Cys His Val Arg Thr Gly Thr Ile Leu Leu Gly Val
 20 25 30
 Trp Tyr Leu Ile Ile Asn Ala Val Val Leu Leu Ile Leu Leu Ser
 35 40 45
 Ala Leu Ala Asp Pro Asp Gln Tyr Asn Phe Ser Ser Ser Glu Leu
 50 55 60
 Gly Gly Asp Phe Glu Phe Met Asp Asp Ala Asn Met Cys Ile Ala
 65 70 75
 Ile Ala Ile Ser Leu Leu Met Ile Leu Ile Cys Ala Met Ala Thr
 80 85 90
 Tyr Gly Ala Tyr Lys Gln Arg Ala Ala Trp Ile Ile Pro Phe Phe
 95 100 105
 Cys Tyr Gln Ile Phe Asp Phe Ala Leu Asn Met Leu Val Ala Ile
 110 115 120
 Thr Val Leu Ile Tyr Pro Asn Ser Ile Gln Glu Tyr Ile Arg Gln
 125 130 135
 Leu Pro Pro Asn Phe Pro Tyr Arg Asp Asp Val Met Ser Val Asn
 140 145 150
 Pro Thr Cys Leu Val Leu Ile Ile Leu Leu Phe Ile Ser Ile Ile
 155 160 165
 Leu Thr Phe Lys Gly Tyr Leu Ile Ser Cys Val Trp Asn Cys Tyr
 170 175 180
 Arg Tyr Ile Asn Gly Arg Asn Ser Ser Asp Val Leu Val Tyr Val
 185 190 195
 Thr Ser Asn Asp Thr Thr Val Leu Leu Pro Pro Tyr Asp Asp Ala
 200 205 210
 Thr Val Asn Gly Ala Ala Lys Glu Pro Pro Pro Pro Tyr Val Ser
 215 220 225
 Ala

<210> 27
 <211> 136
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 3255825CD1

<400> 27
 Met Ile Ser Ile Thr Glu Trp Gln Lys Ile Gly Val Gly Ile Thr
 1 5 10 15
 Gly Phe Gly Ile Phe Phe Ile Leu Phe Gly Thr Leu Leu Tyr Phe
 20 25 30
 Asp Ser Val Leu Leu Ala Phe Gly Asn Leu Leu Phe Leu Thr Gly
 35 40 45
 Leu Ser Leu Ile Ile Gly Leu Arg Lys Thr Phe Trp Phe Phe Phe
 50 55 60
 Gln Arg His Lys Leu Lys Gly Thr Ser Phe Leu Leu Gly Gly Val
 65 70 75

Val	Ile	Val	Leu	Leu	Arg	Trp	Pro	Leu	Leu	Gly	Met	Phe	Leu	Glu
			80						85					90
Thr	Tyr	Gly	Phe	Phe	Ser	Leu	Phe	Lys	Gly	Phe	Phe	Pro	Val	Ala
			95						100					105
Phe	Gly	Ser	Trp	Ala	Met	Ser	Ala	Thr	Ser	Pro	Ser	Trp	Val	Arg
			110						115					120
Cys	Ser	Gly	Asp	Phe	Lys	Ala	Leu	Ala	Arg	Trp	Ser	Glu	Lys	Gln
			125						130					135

Arg

<210> 28

<211> 458

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3393430CD1

<400> 28

Met	Ala	Trp	Ala	Ser	Arg	Leu	Gly	Leu	Leu	Leu	Ala	Leu	Leu	Leu
1				5					10					15
Pro	Val	Val	Gly	Ala	Ser	Thr	Pro	Gly	Thr	Val	Val	Arg	Leu	Asn
				20					25					30
Lys	Ala	Ala	Leu	Ser	Tyr	Val	Ser	Glu	Ile	Gly	Lys	Ala	Pro	Leu
				35					40					45
Gln	Arg	Ala	Leu	Gln	Val	Thr	Val	Pro	His	Phe	Leu	Asp	Trp	Ser
				50					55					60
Gly	Glu	Ala	Leu	Gln	Pro	Thr	Arg	Ile	Arg	Ile	Leu	Asn	Val	His
				65					70					75
Val	Pro	Arg	Leu	His	Leu	Lys	Phe	Ile	Ala	Gly	Phe	Gly	Val	Arg
				80					85					90
Leu	Leu	Ala	Ala	Ala	Asn	Phe	Thr	Phe	Lys	Val	Phe	Arg	Ala	Pro
				95					100					105
Glu	Pro	Leu	Glu	Leu	Thr	Leu	Pro	Val	Glu	Leu	Leu	Ala	Asp	Thr
				110					115					120
Arg	Val	Thr	Gln	Ser	Ser	Ile	Arg	Thr	Pro	Val	Val	Ser	Ile	Ser
				125					130					135
Ala	Cys	Ser	Leu	Phe	Ser	Gly	His	Ala	Asn	Glu	Phe	Asp	Gly	Ser
				140					145					150
Asn	Ser	Thr	Ser	His	Ala	Leu	Leu	Val	Leu	Val	Gln	Lys	His	Ile
				155					160					165
Lys	Ala	Val	Leu	Ser	Asn	Lys	Leu	Cys	Leu	Ser	Ile	Ser	Asn	Leu
				170					175					180
Val	Gln	Gly	Val	Asn	Val	His	Leu	Gly	Thr	Leu	Ile	Gly	Leu	Asn
				185					190					195
Pro	Val	Gly	Pro	Glu	Ser	Gln	Ile	Arg	Tyr	Ser	Met	Val	Ser	Val
				200					205					210
Pro	Thr	Val	Thr	Ser	Asp	Tyr	Ile	Ser	Leu	Glu	Val	Asn	Ala	Val
				215					220					225
Leu	Phe	Leu	Leu	Gly	Lys	Pro	Ile	Ile	Leu	Pro	Thr	Asp	Ala	Thr
				230					235					240
Pro	Phe	Val	Leu	Pro	Arg	His	Val	Gly	Thr	Glu	Gly	Ser	Met	Ala
				245					250					255
Thr	Val	Gly	Leu	Ser	Gln	Gln	Leu	Phe	Asp	Ser	Ala	Leu	Leu	Leu
				260					265					270
Leu	Gln	Lys	Ala	Gly	Ala	Leu	Asn	Leu	Asp	Ile	Thr	Gly	Gln	Leu
				275					280					285
Arg	Ser	Asp	Asp	Asn	Leu	Leu	Asn	Thr	Ser	Ala	Leu	Gly	Arg	Leu
				290					295					300
Ile	Pro	Glu	Val	Ala	Arg	Gln	Phe	Pro	Glu	Pro	Met	Pro	Val	Val
				305					310					315
Leu	Lys	Val	Arg	Leu	Gly	Ala	Thr	Pro	Val	Ala	Met	Leu	His	Thr

Asn Asn Ala Thr	320	325	330
Leu Arg Leu Gln Pro Phe Val Glu Val Leu Ala			
335	340	345	
Thr Ala Ser Asn Ser Ala Phe Gln Ser Leu Phe Ser Leu Asp Val			
350	355	360	
Val Val Asn Leu Arg Leu Gln Leu Ser Val Ser Lys Val Lys Leu			
365	370	375	
Gln Gly Thr Thr Ser Val Leu Gly Asp Val Gln Leu Thr Val Ala			
380	385	390	
Ser Ser Asn Val Gly Phe Ile Asp Thr Asp Gln Val Arg Thr Leu			
395	400	405	
Met Gly Thr Val Phe Glu Lys Pro Leu Leu Asp His Leu Asn Ala			
410	415	420	
Leu Leu Ala Met Gly Ile Ala Leu Pro Gly Val Val Asn Leu His			
425	430	435	
Tyr Val Ala Pro Glu Ile Phe Val Tyr Glu Gly Tyr Val Val Ile			
440	445	450	
Ser Ser Gly Leu Phe Tyr Gln Ser			
455			

<210> 29

<211> 368

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3490990CD1

<400> 29

Met Phe Gly Gln Asn Leu Glu Val Gln Leu Ser Ser Ala Arg Thr		
1 5 10 15		
Glu Asn Thr Thr Val Val Trp Lys Ser Phe His Asp Ser Ile Thr		
20 25 30		
Leu Ile Val Leu Ser Ser Glu Val Gly Ile Ser Glu Leu Arg Leu		
35 40 45		
Glu Arg Leu Leu Gln Met Val Phe Gly Ala Met Val Leu Leu Val		
50 55 60		
Gly Leu Glu Glu Leu Thr Asn Ile Arg Asn Val Glu Arg Leu Lys		
65 70 75		
Lys Asp Leu Arg Ala Ser Tyr Cys Leu Ile Asp Ser Phe Leu Gly		
80 85 90		
Asp Ser Glu Leu Ile Gly Asp Leu Thr Gln Cys Val Asp Cys Val		
95 100 105		
Ile Pro Pro Glu Gly Ser Leu Leu Gln Glu Ala Leu Ser Gly Phe		
110 115 120		
Ala Glu Ala Ala Gly Thr Thr Phe Val Ser Leu Val Val Ser Gly		
125 130 135		
Arg Val Val Ala Ala Thr Glu Gly Trp Trp Arg Leu Gly Thr Pro		
140 145 150		
Glu Ala Val Leu Leu Pro Trp Leu Val Gly Ser Leu Pro Pro Gln		
155 160 165		
Thr Ala Arg Asp Tyr Pro Val Tyr Leu Pro His Gly Ser Pro Thr		
170 175 180		
Val Pro His Arg Leu Leu Thr Leu Thr Leu Leu Pro Ser Leu Glu		
185 190 195		
Leu Cys Leu Leu Cys Gly Pro Ser Pro Pro Leu Ser Gln Leu Tyr		
200 205 210		
Pro Gln Leu Leu Glu Arg Trp Trp Gln Pro Leu Leu Asp Pro Leu		
215 220 225		
Arg Ala Cys Leu Pro Leu Gly Pro Arg Ala Leu Pro Ser Gly Phe		
230 235 240		
Pro Leu His Thr Asp Ile Leu Gly Leu Leu Leu His Leu Glu		
245 250 255		

Leu Lys Arg Cys Leu Phe Thr Val Glu Pro Leu Gly Asp Lys Glu
 260 265 270
 Pro Ser Pro Glu Gln Arg Arg Arg Leu Leu Arg Asn Phe Tyr Thr
 275 280 285
 Leu Val Thr Ser Thr His Phe Pro Pro Glu Pro Gly Pro Pro Glu
 290 295 300
 Lys Thr Glu Asp Glu Val Tyr Gln Ala Gln Leu Pro Arg Ala Cys
 305 310 315
 Tyr Leu Val Leu Gly Thr Glu Glu Pro Gly Thr Gly Val Arg Leu
 320 325 330
 Val Ala Leu Gln Leu Gly Leu Arg Arg Leu Leu Leu Leu Ser
 335 340 345
 Pro Gln Ser Pro Thr His Gly Leu Arg Ser Leu Ala Thr His Thr
 350 355 360
 Leu His Ala Leu Thr Pro Leu Leu
 365

<210> 30

<211> 91

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3635154CD1

<400> 30

Met Tyr Gly Lys Ile Ile Phe Val Leu Leu Leu Ser Glu Ile Val
 1 5 10 15
 Ser Ile Ser Ala Ser Ser Thr Thr Gly Val Ala Met His Thr Ser
 20 25 30
 Thr Ser Ser Ser Val Thr Lys Ser Tyr Ile Ser Ser Gln Thr Asn
 35 40 45
 Gly Glu Thr Gly Gln Leu Val His Arg Phe Thr Val Pro Ala Pro
 50 55 60
 Val Val Ile Ile Leu Ile Ile Leu Cys Val Met Ala Gly Ile Ile
 65 70 75
 Gly Thr Ile Leu Leu Phe Ser Tyr Ser Phe Arg Arg Leu Ile Lys
 80 85 90
 Gly

<210> 31

<211> 295

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 4374347CD1

<400> 31

Met Gly Pro Pro Ser Ala Cys Pro His Arg Glu Cys Ile Pro Trp
 1 5 10 15
 Gln Gly Leu Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Ala
 20 25 30
 Pro Thr Thr Ala Trp Leu Phe Ile Ala Ser Ala Pro Phe Glu Val
 35 40 45
 Ala Glu Gly Glu Asn Val His Leu Ser Val Val Tyr Leu Pro Glu
 50 55 60
 Asn Leu Tyr Ser Tyr Gly Trp Tyr Lys Gly Lys Thr Val Glu Pro
 65 70 75
 Asn Gln Leu Ile Ala Ala Tyr Val Ile Asp Thr His Val Arg Thr
 80 85 90
 Pro Gly Pro Ala Tyr Ser Gly Arg Glu Thr Ile Ser Pro Ser Gly

	95		100		105
Asp Leu His Phe	Gln Asn Val Thr Leu	Glu Asp Thr Gly Tyr Tyr			
	110		115		120
Asn Leu Gln Val	Thr Tyr Arg Asn Ser	Gln Ile Glu Gln Ala Ser			
	125		130		135
His His Leu Arg	Val Tyr Glu Ser Val	Ala Gln Pro Ser Ile Gln			
	140		145		150
Ala Ser Ser Thr	Thr Val Thr Glu Lys	Gly Ser Val Val Leu Thr			
	155		160		165
Cys His Thr Asn	Asn Thr Gly Thr Ser	Phe Gln Trp Ile Phe Asn			
	170		175		180
Asn Gln Arg Leu	Gln Val Thr Lys Arg	Met Lys Leu Ser Trp Phe			
	185		190		195
Asn His Val Leu	Thr Ile Asp Pro Ile	Arg Gln Glu Asp Ala Gly			
	200		205		210
Glu Tyr Gln Cys	Glu Val Ser Asn Pro	Val Ser Ser Asn Arg Ser			
	215		220		225
Asp Pro Leu Lys	Leu Thr Val Lys Tyr	Asp Asn Thr Leu Gly Ile			
	230		235		240
Leu Ile Gly Val	Leu Val Gly Ser Leu	Leu Val Ala Ala Leu Val			
	245		250		255
Cys Phe Leu Leu	Leu Arg Lys Thr Gly	Arg Ala Ser Asp Gln Ser			
	260		265		270
Asp Phe Arg Glu	Gln Gln Pro Pro Ala	Ser Thr Pro Gly His Gly			
	275		280		285
Pro Ser Asp Ser	Ser Asp Ser Ser Ile	Ser			
	290		295		

<210> 32

<211> 724

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 4596747CD1

<400> 32

Met Phe Asp Thr	Thr Pro His Ser Gly	Arg Ser Thr Pro Ser Ser
1	5	10
Ser Pro Ser Leu	Arg Lys Arg Leu Gln	Leu Leu Pro Pro Ser Arg
	20	25
Pro Pro Pro Glu	Pro Glu Pro Gly Thr	Met Val Glu Lys Gly Ser
	35	40
Asp Ser Ser Ser	Glu Lys Gly Gly Val	Pro Gly Thr Pro Ser Thr
	50	55
Gln Ser Leu Gly	Ser Arg Asn Phe Ile	Arg Asn Ser Lys Lys Met
	65	70
Gln Ser Trp Tyr	Ser Met Leu Ser Pro	Thr Tyr Lys Gln Arg Asn
	80	85
Glu Asp Phe Arg	Lys Leu Phe Ser Lys	Leu Pro Glu Ala Glu Arg
	95	100
Leu Ile Val Asp	Tyr Ser Cys Ala Leu	Gln Arg Glu Ile Leu Leu
	110	115
Gln Gly Arg Leu	Tyr Leu Ser Glu Asn	Trp Ile Cys Phe Tyr Ser
	125	130
Asn Ile Phe Arg	Trp Glu Thr Thr Ile	Ser Ile Gln Leu Lys Glu
	140	145
Val Thr Cys Leu	Lys Lys Glu Lys Thr	Ala Lys Leu Ile Pro Asn
	155	160
Ala Ile Gln Ile	Cys Thr Glu Ser Glu	Lys His Phe Phe Thr Ser
	170	175
Phe Gly Ala Arg	Asp Arg Cys Phe Leu	Leu Ile Phe Arg Leu Trp
	185	190

Gln	Asn	Ala	Leu	Leu	Glu	Lys	Thr	Leu	Ser	Pro	Arg	Glu	Leu	Trp
				200					205					210
His	Leu	Val	His	Gln	Cys	Tyr	Gly	Ser	Glu	Leu	Gly	Leu	Thr	Ser
				215					220					225
Glu	Asp	Glu	Asp	Tyr	Val	Ser	Pro	Leu	Gln	Leu	Asn	Gly	Leu	Gly
				230					235					240
Thr	Pro	Lys	Glu	Val	Gly	Asp	Val	Ile	Ala	Leu	Ser	Asp	Ile	Thr
				245					250					255
Ser	Ser	Gly	Ala	Ala	Asp	Arg	Ser	Gln	Glu	Pro	Ser	Pro	Val	Gly
				260					265					270
Ser	Arg	Arg	Gly	His	Val	Thr	Pro	Asn	Leu	Ser	Arg	Ala	Ser	Ser
				275					280					285
Asp	Ala	Asp	His	Gly	Ala	Glu	Glu	Asp	Lys	Glu	Glu	Gln	Val	Asp
				290					295					300
Ser	Gln	Pro	Asp	Ala	Ser	Ser	Ser	Gln	Thr	Val	Thr	Pro	Val	Ala
				305					310					315
Glu	Pro	Pro	Ser	Thr	Glu	Pro	Thr	Gln	Pro	Asp	Gly	Pro	Thr	Thr
				320					325					330
Leu	Gly	Pro	Leu	Asp	Leu	Leu	Pro	Ser	Glu	Glu	Leu	Leu	Thr	Asp
				335					340					345
Thr	Ser	Asn	Ser	Ser	Ser	Ser	Thr	Gly	Glu	Glu	Ala	Asp	Leu	Ala
				350					355					360
Ala	Leu	Leu	Pro	Asp	Leu	Ser	Gly	Arg	Leu	Leu	Ile	Asn	Ser	Val
				365					370					375
Phe	His	Val	Gly	Ala	Glu	Arg	Leu	Gln	Gln	Met	Leu	Phe	Ser	Asp
				380					385					390
Ser	Pro	Phe	Leu	Gln	Gly	Phe	Leu	Gln	Gln	Cys	Lys	Phe	Thr	Asp
				395					400					405
Val	Thr	Leu	Ser	Pro	Trp	Ser	Gly	Asp	Ser	Lys	Cys	His	Gln	Arg
				410					415					420
Arg	Val	Leu	Thr	Tyr	Thr	Ile	Pro	Ile	Ser	Asn	Pro	Leu	Gly	Pro
				425					430					435
Lys	Ser	Ala	Ser	Val	Val	Glu	Thr	Gln	Thr	Leu	Phe	Arg	Arg	Gly
				440					445					450
Pro	Gln	Ala	Gly	Gly	Cys	Val	Val	Asp	Ser	Glu	Val	Leu	Thr	Gln
				455					460					465
Gly	Ile	Pro	Tyr	Gln	Asp	Tyr	Phe	Tyr	Thr	Ala	His	Arg	Tyr	Cys
				470					475					480
Ile	Leu	Gly	Leu	Ala	Arg	Asn	Lys	Ala	Arg	Leu	Arg	Val	Ser	Ser
				485					490					495
Glu	Ile	Arg	Tyr	Arg	Lys	Gln	Pro	Trp	Ser	Leu	Val	Lys	Ser	Leu
				500					505					510
Ile	Glu	Lys	Asn	Ser	Trp	Ser	Gly	Ile	Glu	Asp	Tyr	Phe	His	His
				515					520					525
Leu	Glu	Arg	Glu	Leu	Ala	Lys	Ala	Glu	Lys	Leu	Ser	Leu	Glu	Glu
				530					535					540
Gly	Gly	Lys	Asp	Ala	Arg	Gly	Leu	Leu	Ser	Gly	Leu	Arg	Arg	Arg
				545					550					555
Lys	Arg	Pro	Leu	Ser	Trp	Arg	Ala	His	Gly	Asp	Gly	Pro	Gln	His
				560					565					570
Pro	Asp	Pro	Asp	Pro	Cys	Ala	Arg	Ala	Gly	Ile	His	Thr	Ser	Gly
				575					580					585
Ser	Leu	Ser	Ser	Arg	Phe	Ser	Glu	Pro	Ser	Val	Asp	Gln	Gly	Pro
				590					595					600
Gly	Ala	Gly	Ile	Pro	Ser	Ala	Leu	Val	Leu	Ile	Ser	Ile	Val	Ile
				605					610					615
Cys	Val	Ser	Leu	Ile	Ile	Leu	Ile	Ala	Leu	Asn	Val	Leu	Leu	Phe
				620					625					630
Tyr	Arg	Leu	Trp	Ser	Leu	Glu	Arg	Thr	Ala	His	Thr	Phe	Glu	Ser
				635					640					645
Trp	His	Ser	Leu	Ala	Leu	Ala	Lys	Gly	Lys	Phe	Pro	Gln	Thr	Ala
				650					655					660
Thr	Glu	Trp	Ala	Glu	Ile	Leu	Ala	Leu	Gln	Lys	Gln	Phe	His	Ser

	665		670		675
Val Glu Val His	Lys Trp Arg Gln Ile	Leu Arg Ala Ser Val	Glu		
	680		685		690
Leu Leu Asp Glu	Met Lys Phe Ser Leu	Glu Lys Leu His Gln	Gly		
	695		700		705
Ile Thr Val Ser	Asp Pro Pro Phe Asp	Thr Gln Pro Arg Pro	Asp		
	710		715		720
Asp Ser Phe Ser					

<210> 33
 <211> 331
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 5052680CD1

<400> 33

Met Arg Pro Ala	Leu Ala Val Gly	Leu Val Phe Ala Gly	Cys Cys
1	5	10	15
Ser Asn Val Ile	Phe Leu Glu Leu	Leu Ala Arg Lys His	Pro Gly
	20	25	30
Cys Gly Asn Ile	Val Thr Phe Ala Gln	Phe Leu Phe Ile Ala	Val
	35	40	45
Glu Gly Phe Leu	Phe Glu Ala Asp	Leu Gly Arg Lys Pro	Pro Ala
	50	55	60
Ile Pro Ile Arg	Tyr Tyr Ala Ile	Met Val Thr Met Phe	Phe Thr
	65	70	75
Val Ser Val Val	Asn Asn Tyr Ala	Leu Asn Leu Asn Ile	Ala Met
	80	85	90
Pro Leu His Met	Ile Phe Arg Ser	Gly Ser Leu Ile Ala	Asn Met
	95	100	105
Ile Leu Gly Ile	Ile Ile Leu Lys	Lys Arg Tyr Ser Ile	Phe Lys
	110	115	120
Tyr Thr Ser Ile	Ala Leu Val Ser	Val Gly Ile Phe Ile	Cys Thr
	125	130	135
Phe Met Ser Ala	Lys Gln Val Thr	Ser Gln Ser Ser Leu	Ser Glu
	140	145	150
Asn Asp Gly Phe	Gln Ala Phe Val	Trp Trp Leu Leu Gly	Ile Gly
	155	160	165
Ala Leu Thr Phe	Ala Leu Leu Met	Ser Ala Arg Met Gly	Ile Phe
	170	175	180
Gln Glu Thr Leu	Tyr Lys Arg Phe	Gly Lys His Ser Lys	Glu Ala
	185	190	195
Leu Phe Tyr Asn	His Ala Leu Pro	Leu Pro Gly Phe Val	Phe Leu
	200	205	210
Ala Ser Asp Ile	Tyr Asp His Ala	Val Leu Phe Asn Lys	Ser Glu
	215	220	225
Leu Tyr Glu Ile	Pro Val Ile Gly	Val Thr Leu Pro Ile	Met Trp
	230	235	240
Phe Tyr Leu Leu	Met Asn Ile Ile	Thr Gln Tyr Val Cys	Ile Arg
	245	250	255
Gly Val Phe Ile	Leu Thr Thr Glu	Cys Ala Ser Leu Thr	Val Thr
	260	265	270
Leu Val Val Thr	Leu Arg Lys Phe	Val Ser Leu Ile Phe	Ser Ile
	275	280	285
Leu Tyr Phe Gln	Asn Pro Phe Thr	Leu Trp His Trp Leu	Gly Thr
	290	295	300
Leu Phe Val Phe	Ile Gly Thr Leu	Met Tyr Thr Glu Val	Trp Asn
	305	310	315
Asn Leu Gly Thr	Thr Lys Ser Glu	Pro Gln Lys Asp Ser	Lys Lys
	320	325	330

Asn

<210> 34

<211> 398

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 5373575CD1

<400> 34

Met	Leu	Gly	Arg	Ser	Gly	Tyr	Arg	Ala	Leu	Pro	Leu	Gly	Asp	Phe
1				5					10					15
Asp	Arg	Phe	Gln	Gln	Ser	Ser	Phe	Gly	Phe	Leu	Gly	Ser	Gln	Lys
			20						25					30
Gly	Cys	Leu	Ser	Pro	Glu	Arg	Gly	Gly	Val	Gly	Thr	Gly	Ala	Asp
			35						40					45
Val	Pro	Gln	Ser	Trp	Pro	Ser	Cys	Leu	Cys	His	Gly	Leu	Ile	Ser
			50						55					60
Phe	Leu	Gly	Phe	Leu	Leu	Leu	Val	Thr	Phe	Pro	Ile	Ser	Gly	
			65						70					75
Trp	Phe	Ala	Leu	Lys	Ile	Val	Pro	Thr	Tyr	Glu	Arg	Met	Ile	Val
			80						85					90
Phe	Arg	Leu	Gly	Arg	Ile	Arg	Thr	Pro	Gln	Gly	Pro	Gly	Met	Val
			95						100					105
Leu	Leu	Leu	Pro	Phe	Ile	Asp	Ser	Phe	Gln	Arg	Val	Asp	Leu	Arg
			110						115					120
Thr	Arg	Ala	Phe	Asn	Val	Pro	Pro	Cys	Lys	Leu	Ala	Ser	Lys	Asp
			125						130					135
Gly	Ala	Val	Leu	Ser	Val	Gly	Ala	Asp	Val	Gln	Phe	Arg	Ile	Trp
			140						145					150
Asp	Pro	Val	Leu	Ser	Val	Met	Thr	Val	Lys	Asp	Leu	Asn	Thr	Ala
			155						160					165
Thr	Arg	Met	Thr	Ala	Gln	Asn	Ala	Met	Thr	Lys	Ala	Leu	Leu	Lys
			170						175					180
Arg	Pro	Leu	Arg	Glu	Ile	Gln	Met	Glu	Lys	Leu	Lys	Ile	Ser	Asp
			185						190					195
Gln	Leu	Leu	Leu	Glu	Ile	Asn	Asp	Val	Thr	Arg	Ala	Trp	Gly	Leu
			200						205					210
Glu	Val	Asp	Arg	Val	Glu	Leu	Ala	Val	Glu	Ala	Val	Leu	Gln	Pro
			215						220					225
Pro	Gln	Asp	Ser	Pro	Ala	Gly	Pro	Asn	Leu	Asp	Ser	Thr	Leu	Gln
			230						235					240
Gln	Leu	Ala	Leu	His	Phe	Leu	Gly	Gly	Ser	Met	Asn	Ser	Met	Ala
			245						250					255
Gly	Gly	Ala	Pro	Ser	Pro	Gly	Pro	Ala	Asp	Thr	Val	Glu	Met	Val
			260						265					270
Ser	Glu	Val	Glu	Pro	Pro	Ala	Pro	Gln	Val	Gly	Ala	Arg	Ser	Ser
			275						280					285
Pro	Lys	Gln	Pro	Leu	Ala	Glu	Gly	Leu	Leu	Thr	Ala	Leu	Gln	Pro
			290						295					300
Phe	Leu	Ser	Glu	Ala	Leu	Val	Ser	Gln	Val	Gly	Ala	Cys	Tyr	Gln
			305						310					315
Phe	Asn	Val	Val	Leu	Pro	Ser	Gly	Thr	Gln	Ser	Ala	Tyr	Phe	Leu
			320						325					330
Asp	Leu	Thr	Thr	Gly	Arg	Gly	Arg	Val	Gly	His	Gly	Val	Pro	Asp
			335						340					345
Gly	Ile	Pro	Asp	Val	Val	Val	Glu	Met	Ala	Glu	Ala	Asp	Leu	Arg
			350						355					360
Ala	Leu	Leu	Cys	Arg	Glu	Leu	Arg	Pro	Leu	Gly	Ala	Tyr	Met	Ser
			365						370					375
Gly	Arg	Leu	Lys	Val	Lys	Gly	Asp	Leu	Ala	Met	Ala	Met	Lys	Leu

380
Glu Ala Val Leu Arg Ala Leu Lys
395

385

390

<210> 35
<211> 220
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 5524468CD1

<400> 35
Met Thr Trp Leu Val Leu Leu Gly Thr Leu Leu Cys Met Leu Arg
1 5 10 15
Val Gly Leu Gly Thr Pro Asp Ser Glu Gly Phe Pro Pro Arg Ala
20 25 30
Leu His Asn Cys Pro Tyr Lys Cys Ile Cys Ala Ala Asp Leu Leu
35 40 45
Ser Cys Thr Gly Leu Gly Leu Gln Asp Val Pro Ala Glu Leu Pro
50 55 60
Ala Ala Thr Ala Asp Leu Asp Leu Ser His Asn Ala Leu Gln Arg
65 70 75
Leu Arg Pro Gly Trp Leu Ala Pro Leu Phe Gln Leu Arg Ala Leu
80 85 90
His Leu Asp His Asn Glu Leu Asp Ala Leu Gly Arg Gly Val Phe
95 100 105
Val Asn Ala Ser Gly Leu Arg Leu Leu Asp Leu Ser Ser Asn Thr
110 115 120
Leu Arg Ala Leu Gly Arg His Asp Leu Asp Gly Leu Gly Ala Leu
125 130 135
Glu Lys Leu Leu Leu Phe Asn Asn Arg Leu Val His Leu Asp Glu
140 145 150
His Ala Phe His Gly Leu Arg Ala Leu Ser His Leu Tyr Leu Gly
155 160 165
Cys Asn Glu Leu Ala Ser Phe Ser Phe Asp His Leu His Gly Leu
170 175 180
Ser Ala Thr His Leu Leu Thr Leu Asp Leu Ser Ser Asn Arg Leu
185 190 195
Gly His Ile Ser Val Pro Glu Leu Ala Ala Leu Pro Ala Phe Leu
200 205 210
Lys Asn Gly Leu Tyr Leu His Asp Asn Thr
215 220

<210> 36
<211> 706
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 5944279CD1

<400> 36
Met Glu Glu Asn Pro Thr Leu Glu Ser Glu Ala Trp Gly Ser Ser
1 5 10 15
Arg Gly Trp Leu Ala Pro Arg Glu Ala Arg Gly Gly Pro Ser Leu
20 25 30
Ser Ser Val Leu Asn Glu Leu Pro Ser Ala Ala Thr Leu Arg Tyr
35 40 45
Arg Asp Pro Gly Val Leu Pro Trp Gly Ala Leu Glu Glu Glu Glu
50 55 60
Glu Asp Gly Gly Arg Ser Arg Lys Ala Phe Thr Glu Val Thr Gln
65 70 75

Thr	Glu	Leu	Gln	Asp	Pro	His	Pro	Ser	Arg	Glu	Leu	Pro	Trp	Pro	
				80					85					90	
Met	Gln	Ala	Arg	Arg	Ala	His	Arg	Gln	Arg	Asn	Ala	Ser	Arg	Asp	
				95					100					105	
Gln	Val	Val	Tyr	Gly	Ser	Gly	Thr	Lys	Thr	Asp	Arg	Trp	Ala	Arg	
				110					115					120	
Leu	Leu	Arg	Arg	Ser	Lys	Glu	Lys	Thr	Lys	Glu	Gly	Leu	Arg	Ser	
				125					130					135	
Leu	Gln	Pro	Trp	Ala	Trp	Thr	Leu	Lys	Arg	Ile	Gly	Gly	Gln	Phe	
				140					145					150	
Gly	Ala	Gly	Thr	Glu	Ser	Tyr	Phe	Ser	Leu	Leu	Arg	Phe	Leu	Leu	
				155					160					165	
Leu	Leu	Asn	Val	Leu	Ala	Ser	Val	Leu	Met	Ala	Cys	Met	Thr	Leu	
				170					175					180	
Leu	Pro	Thr	Trp	Leu	Gly	Gly	Ala	Pro	Pro	Gly	Pro	Pro	Gly	Pro	
				185					190					195	
Asp	Ile	Ser	Ser	Pro	Cys	Gly	Ser	Tyr	Asn	Pro	His	Ser	Gln	Gly	
				200					205					210	
Leu	Val	Thr	Phe	Ala	Thr	Gln	Leu	Phe	Asn	Leu	Leu	Ser	Gly	Glu	
				215					220					225	
Gly	Tyr	Leu	Glu	Trp	Ser	Pro	Leu	Phe	Tyr	Gly	Phe	Tyr	Pro	Pro	
				230					235					240	
Arg	Pro	Arg	Leu	Ala	Val	Thr	Tyr	Leu	Cys	Trp	Ala	Phe	Ala	Val	
				245					250					255	
Gly	Leu	Ile	Cys	Leu	Leu	Leu	Ile	Leu	His	Arg	Ser	Val	Ser	Gly	
				260					265					270	
Leu	Lys	Gln	Thr	Leu	Leu	Ala	Glu	Ser	Glu	Ala	Leu	Thr	Ser	Tyr	
				275					280					285	
Ser	His	Arg	Val	Phe	Ser	Ala	Trp	Asp	Phe	Gly	Leu	Cys	Gly	Asp	
				290					295					300	
Val	His	Val	Arg	Leu	Arg	Gln	Arg	Ile	Ile	Leu	Tyr	Glu	Leu	Lys	
				305					310					315	
Val	Glu	Leu	Glu	Glu	Thr	Val	Val	Arg	Arg	Gln	Ala	Ala	Val	Arg	
				320					325					330	
Thr	Leu	Gly	Gln	Gln	Ala	Arg	Val	Trp	Leu	Val	Arg	Val	Leu	Leu	
				335					340					345	
Asn	Leu	Leu	Val	Val	Ala	Leu	Leu	Gly	Ala	Ala	Phe	Tyr	Gly	Val	
				350					355					360	
Tyr	Trp	Ala	Thr	Gly	Cys	Thr	Val	Glu	Leu	Gln	Glu	Met	Pro	Leu	
				365					370					375	
Val	Gln	Glu	Leu	Pro	Leu	Leu	Lys	Leu	Gly	Val	Asn	Tyr	Leu	Pro	
				380					385					390	
Ser	Ile	Phe	Ile	Ala	Gly	Val	Asn	Phe	Val	Leu	Pro	Pro	Val	Phe	
				395					400					405	
Lys	Leu	Ile	Ala	Pro	Leu	Glu	Gly	Tyr	Thr	Arg	Ser	Arg	Gln	Ile	
				410					415					420	
Val	Phe	Ile	Leu	Leu	Arg	Thr	Val	Phe	Leu	Arg	Leu	Ala	Ser	Leu	
				425					430					435	
Val	Val	Leu	Leu	Phe	Ser	Leu	Trp	Asn	Gln	Ile	Thr	Cys	Gly	Gly	
				440					445					450	
Asp	Ser	Glu	Ala	Glu	Asp	Cys	Lys	Thr	Cys	Gly	Tyr	Asn	Tyr	Lys	
				455					460					465	
Gln	Leu	Pro	Cys	Trp	Glu	Thr	Val	Leu	Gly	Gln	Glu	Met	Tyr	Lys	
				470					475					480	
Leu	Leu	Leu	Phe	Asp	Leu	Leu	Thr	Val	Leu	Ala	Val	Ala	Leu	Leu	
				485					490					495	
Ile	Gln	Phe	Pro	Arg	Lys	Leu	Leu	Cys	Gly	Leu	Cys	Pro	Gly	Ala	
				500					505					510	
Leu	Gly	Arg	Leu	Ala	Gly	Thr	Gln	Glu	Phe	Gln	Val	Pro	Asp	Glu	
				515					520					525	
Val	Leu	Gly	Leu	Ile	Tyr	Ala	Gln	Thr	Val	Val	Trp	Val	Gly	Ser	
				530					535					540	
Phe	Phe	Cys	Pro	Leu	Leu	Pro	Leu	Leu	Asn	Thr	Val	Lys	Phe	Leu	

545	550	555
Leu Leu Phe Tyr	Leu Lys Lys Leu Thr	Leu Phe Ser Thr Cys Ser
560	565	570
Pro Ala Ala Arg	Thr Phe Arg Ala Ser	Ala Ala Asn Phe Phe Phe
575	580	585
Pro Leu Val Leu	Leu Leu Gly Leu Ala	Ile Ser Ser Val Pro Leu
590	595	600
Leu Tyr Ser Ile	Phe Leu Ile Pro Pro	Ser Lys Leu Cys Gly Pro
605	610	615
Phe Arg Gly Gln	Ser Ser Ile Trp Ala	Gln Ile Pro Glu Ser Ile
620	625	630
Ser Ser Leu Pro	Glu Thr Thr Gln Asn	Phe Leu Phe Phe Leu Gly
635	640	645
Thr Gln Ala Phe	Ala Val Pro Leu Leu	Leu Ile Ser Ser Ile Leu
650	655	660
Met Ala Tyr Thr	Val Ala Leu Ala Asn	Ser Tyr Gly Arg Leu Ile
665	670	675
Ser Glu Leu Lys	Arg Gln Arg Gln Thr	Glu Ala Gln Asn Lys Val
680	685	690
Phe Leu Ala Arg	Arg Ala Val Ala Leu	Thr Ser Thr Lys Pro Ala
695	700	705

Leu

<210> 37

<211> 466

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 6114480CD1

<400> 37

Met Ala Phe Val	Leu Ile Leu Val	Leu Ser Phe Tyr Glu	Leu Val
1	5	10	15
Ser Gly Gln Trp	Gln Val Thr Gly Pro	Gly Lys Phe Val Gln	Ala
20	25	30	
Leu Val Gly Glu	Asp Ala Val Phe Ser	Cys Ser Leu Phe Pro	Glu
35	40	45	
Thr Ser Ala Glu	Ala Met Glu Val Arg	Phe Phe Arg Asn Gln	Phe
50	55	60	
His Ala Val Val	His Leu Tyr Arg Asp	Gly Glu Asp Trp Glu	Ser
65	70	75	
Lys Gln Met Pro	Gln Tyr Arg Gly Arg	Thr Glu Phe Val Lys	Asp
80	85	90	
Ser Ile Ala Gly	Gly Arg Val Ser Leu	Arg Leu Lys Asn Ile	Thr
95	100	105	
Pro Ser Asp Ile	Gly Leu Tyr Gly Cys	Trp Phe Ser Ser Gln	Ile
110	115	120	
Tyr Asp Glu Glu	Ala Thr Trp Glu Leu	Arg Val Ala Ala Leu	Gly
125	130	135	
Ser Leu Pro Leu	Ile Ser Ile Val Gly	Tyr Val Asp Gly Gly	Ile
140	145	150	
Gln Leu Leu Cys	Leu Ser Ser Gly Trp	Phe Pro Gln Pro Thr	Ala
155	160	165	
Lys Trp Lys Gly	Pro Gln Gly Gln Asp	Leu Ser Ser Asp Ser	Arg
170	175	180	
Ala Asn Ala Asp	Gly Tyr Ser Leu Tyr	Asp Val Glu Ile Ser	Ile
185	190	195	
Ile Val Gln Glu	Asn Ala Gly Ser Ile	Leu Cys Ser Ile His	Leu
200	205	210	
Ala Glu Gln Ser	His Glu Val Glu Ser	Lys Val Leu Ile Gly	Glu
215	220	225	

Thr	Phe	Phe	Gln	Pro	Ser	Pro	Trp	Arg	Leu	Ala	Ser	Ile	Leu	Leu	
				230					235					240	
Gly	Leu	Leu	Cys	Gly	Ala	Leu	Cys	Gly	Val	Val	Met	Gly	Met	Ile	
				245					250					255	
Ile	Val	Phe	Phe	Lys	Ser	Lys	Gly	Lys	Ile	Gln	Ala	Glu	Leu	Asp	
				260					265					270	
Trp	Arg	Arg	Lys	His	Gly	Gln	Ala	Glu	Leu	Arg	Asp	Ala	Arg	Lys	
				275					280					285	
His	Ala	Val	Glu	Val	Thr	Leu	Asp	Pro	Glu	Thr	Ala	His	Pro	Lys	
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				305					310					315	
Gln	Glu	Val	Pro	His	Ser	Glu	Lys	Arg	Phe	Thr	Arg	Lys	Ser	Val	
				320					325					330	
Val	Ala	Ser	Gln	Gly	Phe	Gln	Ala	Gly	Arg	His	Tyr	Trp	Glu	Val	
				335					340					345	
Asp	Val	Gly	Gln	Asn	Val	Gly	Trp	Tyr	Val	Gly	Val	Cys	Arg	Asp	
				350					355					360	
Asp	Val	Asp	Arg	Gly	Lys	Asn	Asn	Val	Thr	Leu	Ser	Pro	Asn	Asn	
				365					370					375	
Gly	Tyr	Trp	Val	Leu	Arg	Leu	Thr	Thr	Glu	His	Leu	Tyr	Phe	Thr	
				380					385					390	
Phe	Asn	Pro	His	Phe	Ile	Ser	Leu	Pro	Pro	Ser	Thr	Pro	Pro	Thr	
				395					400					405	
Arg	Val	Gly	Val	Phe	Leu	Asp	Tyr	Glu	Gly	Gly	Thr	Ile	Ser	Phe	
				410					415					420	
Phe	Asn	Thr	Asn	Asp	Gln	Ser	Leu	Ile	Tyr	Thr	Leu	Leu	Thr	Cys	
				425					430					435	
Gln	Phe	Glu	Gly	Leu	Leu	Arg	Pro	Tyr	Ile	Gln	His	Ala	Met	Tyr	
				440					445					450	
Asp	Glu	Glu	Lys	Gly	Thr	Pro	Ile	Phe	Ile	Cys	Pro	Val	Ser	Trp	
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Gly

<210> 38

<211> 2801

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 112301CB1

<400> 38

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<210> 39

<211> 2656

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 997947CB1

<220>

<221> unsure

<222> 2554, 2587, 2604, 2606, 2611, 2644, 2646-2647, 2651

<223> a, t, c, g, or other

<400> 39

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aagttttttg ggccactgac attgaatgca acaactgatt tcatacaact gaattactct 2460
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<210> 40

<211> 968

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1521513CB1

<400> 40

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aaagagagag agagaaacaa aaaaccaaag agagagaaaa aatgaattca tctaaatcat 180
ctgaaacaca atgcacagag agaggatgct tctcttccca aatgttctta tggactgttg 240
ctgggatccc caccctattt ctcatgacct gtttcatcac cagatgtgtt gtgacatttc 300
gcatctttca aacctgtgat gagaaaaagt ttcatgctac tgagaatttc acagagctct 360
cctgctacaa ttatggatca ggttcagtca agaattgttg tccattgaac tgggaatatt 420
ttcaatccag ctgctacttc ttttctactg acaccatttc ctgggcgtta agtttaaga 480
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acccaaggca aaattggaat gatgtaacct gtttccctcaa ttattttcgg atttgtgaaa 780
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aatgtgtaaa gaaggaagag caagaacatg gccacaccca ccgccccaca cgagaaattt 900
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<210> 41

<211> 1837

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1863994CB1

<400> 41

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<210> 42

<211> 2124

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2071941CB1

<400> 42

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agagacttgg cattcaaaaa aaaa 2124

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<210> 43
 <211> 993
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2172512CB1

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<400> 43
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gcattctgcg gggcaggcgg attaatgga attcttcaaa atgtcagggt tgggtaccac 180
agccctgaa cagcctgcag gtgaaatgga aaatcaaaca aaaccaccag atccaaggcc 240
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<210> 44
 <211> 2214
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2483172CB1

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<210> 45

<211> 897

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2656128CB1

<400> 45

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<210> 46

<211> 2167

<212> DNA

<213> Homo sapiens

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<223> Incyte ID No: 5855841CB1

<400> 46

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<210> 47

<211> 1235

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 603462CB1

<400> 47

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<211> 2257

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 747681CB1

<400> 48

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<210> 49

<211> 2359

<212> DNA

<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 919469CB1

<400> 49

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2359

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<211> 2052
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 977658CB1

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<211> 1939

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1004703CB1

<400> 51

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<210> 52

<211> 1138

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1334051CB1

<400> 52

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<210> 53

<211> 2117

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1336728CB1

<400> 53

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tccttgga aa aaaaaa 2117

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<210> 54

<211> 1495

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1452856CB1

<400> 54

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ctggagccca gcggcggtg tgagagtccg taaggagcag cttccaggat cctgagatcc 180
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<210> 55

<211> 1747

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1562471CB1

<400> 55

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aaaaaaa
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<210> 56

<211> 1473

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1618158CB1

<400> 56

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<210> 57

<211> 1591

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1656935CB1

<400> 57

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<210> 58

<211> 1858

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1859305CB1

<400> 58

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atactggaag agaacaccat tttatctcag gttagtgaag aatcagtgca ggtccctgac 1800
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<210> 59

<211> 1454

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 1949083CB1

<400> 59

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aaataaataat aata

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<210> 60
<211> 2310
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 1996357CB1

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ccctattatt taaaaatggc tcaactgaaa tatatggaga atgtggggta tgcccaagag 180
gacagagaac gaatgcacag aaatattgtc agccttgac agaatctcct gaactttatg 240
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<210> 61
<211> 744
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 2061330CB1

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agtgtagagg tgatcgagtg tggatcaaga actggaacgt agcctctttg tgtccactgt 180

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ggaaaggacc ccagactgtc gttctgagca ctcccaccgc tgtgaaggta gaaggaatcc 240
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caagcccaga caacccctgc agagtgaccc tgaagaagac gacaagccct gctccagtca 360
cacccggaag ctgactggtc cacgcacggc cgaagcctga ggaagctcat catgagattc 420
atthttctta aatthttggac ttatacagta agggcttcaa ctgatcttac tcaaactggg 480
gactgttccc agtgacttca tcaggtcacc gaagtaggac agcaaattaa aacaatcttt 540
ctgttctata gttattatga atgtatggaa acaataaaaag aaacttggtt gtataatgcc 600
actcagtaca aggtatgtag cccgagaaat gaccgacctg atgtgtgtta taacccatct 660
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caagtaaaat aataactaga acag                                     744

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<210> 62
 <211> 1109
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2346947CB1

<220>
 <221> unsure
 <222> 30
 <223> a, t, c, g, or other

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<400> 62
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<210> 63
 <211> 2511
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 2795577CB1

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<400> 63
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<210> 64

<211> 788

<212> DNA

<213> Homo sapiens

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<223> Incyte ID No: 3255825CB1

<400> 64

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aaaaaaaaa

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<210> 65

<211> 1831

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3393430CB1

<400> 65

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<210> 66

<211> 1499

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3490990CB1

<400> 66

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<210> 67

<211> 365

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 3635154CB1

<400> 67

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<211> 1102

<212> DNA

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<221> misc_feature

<223> Incyte ID No: 4374347CB1

<400> 68

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<212> DNA
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<211> 1845
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte ID No: 5052680CB1

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<211> 1940

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<213> Homo sapiens

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<223> Incyte ID No: 5373575CB1

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<211> 880

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

<220>

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<223> Incyte ID No: 5944279CB1

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<211> 2850

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 6114480CB1

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acaagggagc	gaaggaacgc	agaagtggaa				2850

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